Siri | Glimstad

200 Park Avenue, Seventeenth Floor, New York, NY 10166
sirillp.com | P: (212) 532-1091 | F: (646) 417-5967

VIA ELECTRONIC FILING

September 4, 2020

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Commissioner Stephen M. Hahn, M.D.
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION TO REQUIRE CLINICAL TRIAL OF ENGERIX-B AND RECOMBIVAX-HB TO ASSESS THE SAFETY OF THESE PRODUCTS	**:**	**Docket No. _____**

CITIZEN PETITION

This petition is being submitted pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act and Public Health Service Act, the Public Health and Welfare at, *inter alia*, 42 U.S.C. § 262(a)(2)(A)-(C) and 42 U.S.C. § 262(j), and 42 U.S.C. § 300aa-10 *et seq.*, to request that the Commissioner of Food and Drugs (the "**Commissioner**") withdraw or suspend the approval granted by the Food and Drug Administration ("**FDA**") for Engerix-B and Recombivax HB for infants[1] and toddlers until a properly controlled and adequately powered double-blind trial of sufficient duration is conducted to assess the safety of these products as required pursuant to applicable federal statutes and regulations for licensing these products.

The clinical trials relied upon to license these products only assessed safety for up to five days after injection. Therefore, these trials did not comply with the applicable federal statutory and

[1] Excluding infants born to mothers who test positive for HBsAg during pregnancy.

regulatory requirements necessary to prove they were "safe" prior to licensure. *See, e.g.*, 21 U.S.C. § 393 (The FDA "shall promote the public health by … reviewing clinical research and taking appropriate action … [to] protect the public health by ensuring that …. drugs are safe and effective."). Consequently, the FDA must either withdraw or suspend the approval of these products until an appropriate clinical trial is conducted, as required by law, to determine their safety for licensure.

A. Action Requested

1. That the FDA withdraw or suspend the approval for Engerix-B and Recombivax HB for infants[2] and toddlers until a double-blind placebo-controlled trial of sufficient duration[3] is conducted to assess the safety of these products.

B. Statement of Grounds

2. The Centers for Disease Control and Prevention ("**CDC**") Recommended Child and Adolescent Immunization Schedule recommends universal vaccination of all infants with a Hepatitis B vaccine at birth, 1-month of age, and 6-months of age.[4] There are only two Hepatitis B vaccines licensed for administration to newborns: Engerix-B and Recombivax HB.

3. The Informed Consent Action Network ("**ICAN**") is a non-profit organization that advocates for informed consent and disseminates information necessary for same with regard to all medical interventions. In 2017, a supporter of ICAN advised the organization that the clinical trial relied upon by the FDA to license each of the two Hepatitis-B vaccines on the market only reviewed safety for a few days after injection. ICAN found this claim incredible. It assumed the claim was likely false.

4. Indeed, the importance of capturing all potential health issues for a material duration during a clinical trial is reflected in the trials of, for example, the drugs Enbrel[5], Lipitor[6], and Botox,[7] which had safety review periods of 6.6 years, 4.8 years and 51 weeks respectively, each with a placebo control group. As another example, the weight loss drug Belviq, indicated only for adult use, was safety tested in a placebo-controlled trial for two years before being licensed by the FDA.[8]

---

[2] *Id*.

[3] As discussed below, safety should be assessed until the infants and toddlers are at least six years of age so that the rates of autoimmune and neurological disorders, many of which are not diagnosed until childhood, can be assessed.

[4] *See* https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#note-hepb (last visited Sept. 3, 2020).

[5] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf (last visited Sept. 3, 2020).

[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf (last visited Sept. 3, 2020).

[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf (last visited Sept. 3, 2020).

[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf (last visited Sept. 3, 2020). In February 2020 the drug was voluntarily removed from the US market at the request of the FDA due to emerging data showing that people who had taken the drug as part of a large clinical trial had an increased occurrence of cancer five years later. *See also* https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-

5. As the FDA explains in its guidance materials: the clinical trial relied upon for licensure is typically "1 to 4 years"[9] and the duration of a clinical trial should "reflect the product and target condition."[10] The time frame for the safety review should be longer for minors, and in particular for babies and toddlers, since autoimmune, neurological, and developmental disorders will often not be diagnosed until after babies are at least a few years old.[11] Indeed, a 2019 review of 306 pediatric studies, authored by researchers at the FDA and Duke University, explained that, compared to licensing a drug for adults, "data on drug efficacy and safety in children may require an additional 6 years."[12]

6. Moreover, Congress mandated that the FDA only license a drug if its sponsor has proven it to be "safe and effective." *See, e.g.*, 21 U.S.C. § 393. The FDA relies upon clinical trial reports provided by the sponsor of the drug to make this determination. The clinical trial information submitted must be sufficient to demonstrate the product is "safe." *Id*. While there are many ways to demonstrate that a product is safe, five days of post-administration safety data for a product that will be injected into babies is patently insufficient to demonstrate safety.

7. Hence, the claim that Engerix-B and Recombivax HB were licensed by the FDA based on only a few days of safety data after each injection sounded like science fiction. ICAN simply found the claim not credible. That was until ICAN reviewed the package insert for each of these two products issued by their manufacturer and subsequently approved by the FDA, which each described their pre-licensure clinical trials. To ICAN's amazement, they appeared to indicate that safety in these clinical trials was only reviewed for a few days after the injection of each into babies.

8. Hence, on October 12, 2017, ICAN sent a letter[13] to the FDA's parent department, HHS, with the following request:

> All drugs licensed by the FDA undergo long-term double-blind pre-licensure clinical trials during which the rate of adverse reactions in

---

belviq-belviq-xr-lorcaserin-market (last visited Sept. 3, 2020); https://www.health.harvard.edu/blog/weight-loss-drug-belviq-recalled-2020040919439 (last visited Sept. 3, 2020).

[9] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited Sept. 3, 2020).

[10] https://www.fda.gov/media/102332/download (last visited Sept. 3, 2020).

[11] For example, according to the CDC, even for a common neurological disorder such as ADHD, "5 years of age was the average age of diagnosis for children reported as having severe ADHD." https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html (last visited Sept. 3, 2020). As another example, learning disabilities, a group of common developmental issues, are often "identified once a child is in school." https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed (last visited Sept. 3, 2020). Even for asthma, a very common autoimmune condition, whose symptoms are obvious, diagnosis can be difficult for children under 5 years of age because lung function tests aren't accurate before 5 years of age and "[s]ometimes a diagnosis can't be made until later, after months or even years of observing symptoms." https://www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513 (last visited Sept. 3, 2020).

[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/ (last visited Sept. 3, 2020).

[13] https://www.icandecide.org/wp-content/uploads/2019/09/ICAN-HHS-Notice-1.pdf (last visited Sept. 3, 2020).

> the group receiving the drug under review is compared to the rate of adverse reactions in a group receiving an inert placebo, such as a sugar pill or saline injection. … And even with these long-term studies, drugs are still often recalled. …
>
> [Nonetheless], of the two Hepatitis B vaccines licensed by the FDA for injection into one-day-old babies, Merck's was licensed after trials that solicited adverse reactions for *only five days* after vaccination and GlaxoSmithKline's was licensed after trials that solicited adverse reactions for *only four days* after vaccination.[14] …
>
> The 1986 Act expressly requires that you, as the Secretary, "shall make or assure improvements in … the licensing … and research on vaccines, in order to reduce the risks of adverse reactions to vaccines." (42 U.S.C. § 300aa-27(a)(2).) Given this statutory obligation: … **Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life?**[15]

9. HHS, in a response reviewed and approved by the FDA,[16] responded by letter,[17] dated January 18, 2018, to the foregoing question as follows:

> Data relied upon in licensing infant use of hepatitis B vaccines is summarized in the respective package inserts. Furthermore, pediatric data from other countries and in the literature, support the safety of these vaccines in infants. The recommendation for all children to receive these vaccines was made by the Advisory Committee for Immunization Practices. Their reasoning is summarized in a *Morbidity and Mortality Weekly Report* at https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm. Follow-up studies support the safety of infant vaccination with hepatitis B vaccines.[18]

10. After a careful review of HHS and the FDA's response, ICAN responded by letter, dated December 31, 2018,[19] which provided, in relevant part, as follows:

---

[14] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf (last visited Sept. 3, 2020); https://www.fda.gov/media/119403/download (last visited Sept. 3, 2020).

[15] *See* n. 13, *supra.*

[16] https://www.icandecide.org/wp-content/uploads/2020/08/Review-Copy.pdf (last visited Sept. 3, 2020).

[17] https://www.icandecide.org/wp-content/uploads/2019/09/HHS-Response-1.pdf (last visited Sept. 3, 2020).

[18] *Id.*

[19] https://www.icandecide.org/wp-content/uploads/2019/09/ICAN-Reply-1.pdf (last visited Sept. 3, 2020).

In our opening letter, we asked that HHS "Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life."[20]

A. Safety Data for Hepatitis B Licensure is Plainly Deficient

HHS begins its response by stating: "Data relied upon in licensing infant use of hepatitis B vaccine is summarized in the respective package insert."[21] It is troubling that HHS responds to the above request by citing the package inserts when our opening letter explained that these precise package inserts provide that their safety was not monitored for longer than five days after injection.[22] As a result, HHS's response merely affirms the concerns we expressed in our original letter that the Hepatitis B vaccine was inadequately tested for safety prior to licensure.

Recombivax HB's package insert asserts it was deemed safe for children based on a clinical trial in which 147 infants and children (up to 10 years of age) were monitored for five days after vaccination.[23] This trial is useless for assessing the safety of this vaccine for pediatric use (let alone for babies on the first day of life) because the sample size is too small, the safety review period is too short, and there is no placebo control. The safety information in the package insert for Engerix-B is just as inadequate since the clinical trial for this vaccine also had no placebo control and only monitored safety for four days after vaccination.[24]

These package inserts plainly do not support the safety of administering these products to babies. Hence, HHS's assertion that the "Data relied upon in licensing infant use of hepatitis B vaccine is summarized in the respective package insert" is very troubling.

B. Safety of Hepatitis B Recommendation for Babies Plainly Deficient

Aside from the package inserts, HHS's response points to only one other identifiable document to support its claim that the Hepatitis B vaccine is safe for babies – a report from the Advisory Committee on Immunization Practices (**ACIP**) that HHS asserts it relied upon

[20] *See* n. 13, *supra.*

[21] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf (last visited Sept. 3, 2020).

[22] *See* n. 17, *supra*.

[23] *See* n. 17, *supra.*

[24] *Id*.

for its "recommendation for all children to receive these vaccines."[25] Sadly, as with the package inserts, this ACIP report does not support the safety of these vaccines for babies or children. A copy of the report is cited in a footnote to this sentence.[26]

The ACIP report cites seven studies to support its recommendation that every baby in this country receive Hepatitis B vaccine injections at 1-day, 1-month, and 6-months of life.[27] Two of the cited studies only included adult[s] … and therefore provide no useful data to evaluate the safety of injecting newborns.[28] The third was a retrospective study that did not use either of the Hepatitis B vaccines licensed for infants in the United States, excluded children that did not complete the vaccine series and lacked a placebo control.[29] The fourth was a retrospective study of potential neurological events from the Hepatitis B vaccine based on reports submitted to a passive surveillance system … "[in which] underreporting is a well-recognized problem" … [and which] involved "virtually all" adults and did not provide any separate results for infants or children.[30] …

The three remaining studies … were clinical trials. But none … are useful for understanding the safety of injecting Hepatitis B vaccine into babies.[31] First, none of them had a placebo control.[32] Second, none … assessed safety for longer than seven days after vaccination.[33]

Indeed, one study had 122 infants and monitored safety for only 7 days.[34] Another study had 79 children monitored for 5 days.[35] Remarkably, in this study 18 percent of the children experienced a systemic or serious adverse reaction … but, absent a placebo

---

[25] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf (last visited Sept. 3, 2020).

[26] https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm (last visited Sept. 3, 2020).

[27] *Id.*

[28] https://www.ncbi.nlm.nih.gov/pubmed/6810736 (last visited Sept. 3, 2020); https://pubmed.ncbi.nlm.nih.gov/6997738/ (last visited Sept. 3, 2020).

[29] Chen D-S. Control of hepatitis B in Asia: mass immunization program in Taiwan. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:716-9.

[30] https://www.ncbi.nlm.nih.gov/pubmed/2962488 (last visited Sept. 3, 2020).

[31] https://www.ncbi.nlm.nih.gov/pubmed/2952812 (last visited Sept. 3, 2020); *see also* https://pubmed.ncbi.nlm.nih.gov/2943814/ (last visited Sept. 3, 2020); https://www.ncbi.nlm.nih.gov/pubmed/2528292 (last visited Sept. 3, 2020).

[32] *Id.*

[33] *Id.*

[34] https://www.ncbi.nlm.nih.gov/pubmed/2952812 (last visited Sept. 3, 2020).

[35] https://www.ncbi.nlm.nih.gov/pubmed/2943814 (last visited Sept. 3, 2020).

control, the pharmaceutical company paid researchers were left to decide [if they] were related to the vaccine.[36] The final study had 3,000 infants and children but *only* monitored safety on the day of and the third day after vaccination.[37] …

As this shows, even though we asked for the science to support the safety of injecting every newborn with the Hepatitis B vaccine starting on the first day of life, the studies HHS has provided do not support such safety and would not be sufficient to license these products for veterinary use in farm animals. For example, prior to licensure of a vaccine for use in chickens, "Daily observation records are required for at least 21 days after vaccination."[38]

C. Urgent Need for Placebo-Controlled Trial of Hepatitis B Vaccine

The need to assess the safety of each Hepatitis B vaccine in robust clinical trials is manifest. The following is a list of the reported post-marketing adverse reactions added to the package insert for Engerix-B because Merck had a "basis to believe there is a causal relationship between the drug and the occurrence of the adverse event"[39]:

> Abnormal Liver Function Tests; Allergic Reaction; Alopecia; Anaphylactoid Reaction; Anaphylaxis; Angioedema; Apnea; Arthralgia; Arthritis; Asthma-Like Symptoms; Bell's Palsy; Bronchospasm; Conjunctivitis; Dermatologic Reactions; Dyspepsia; Earache; Eczema; Ecchymoses; Encephalitis; Encephalopathy; Erythema Multiforme; Erythema Nodosum; Guillain-Barré Syndrome; Hypersensitivity Syndrome (serum sickness-like with onset days to weeks after vaccination); Hypoesthesia; Keratitis; Lichen Planus; Meningitis; Migraine; Multiple Sclerosis; Myelitis; Neuritis; Neuropathy; Optic Neuritis; Palpitations; Paralysis; Paresis; Paresthesia; Purpura; Seizures; Stevens-Johnson Syndrome; Syncope; Tachycardia; Tinnitus;

[36] *Id*.

[37] https://www.ncbi.nlm.nih.gov/pubmed/2528292 (last visited Sept. 3, 2020).

[38] https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_204.pdf (last visited Sept. 3, 2020).

[39] 21 C.F.R. 201.57

> Transverse Muscular Weakness; Thrombocytopenia; Urticaria; Vasculitis; Vertigo; Visual Disturbances.[40]

And these are the reported post-marketing adverse reactions for Recombivax HB added to its package insert because GSK had a basis to conclude each has a causal relationship with that vaccine:

> Agitation; Alopecia; Anaphylactic/Anaphylactoid Reactions; Arthralgia; Arthritis; Arthritis Pain In Extremity; Autoimmune Diseases; Bell's Palsy; Bronchospasm; Constipation; Conjunctivitis; Dermatologic Reactions; Ecchymoses; Eczema; Elevation Of Liver Enzymes; Encephalitis; Erythema Multiforme; Erythema Nodosum; Exacerbation Of Multiple Sclerosis; Febrile Seizure; Guillain-Barré Syndrome; Herpes Zoster; Hypersensitivity Reactions; Hypersensitivity Syndrome (serum sickness-like with onset days to weeks after vaccination); Hypesthesia; Increased Erythrocyte Sedimentation Rate; Irritability; Lupus-Like Syndrome; Migraine; Multiple Sclerosis; Muscle Weakness; Myelitis Including Transverse Myelitis; Optic Neuritis; Peripheral Neuropathy; Petechiae; Polyarteritis Nodosa; Radiculopathy; Seizure; Stevens-Johnson Syndrome; Somnolence; Syncope; Systemic Lupus Erythematosus (SLE); Tachycardia; Thrombocytopenia; Tinnitus; Urticaria; Urticaria; Uveitis; Vasculitis; Visual Disturbances.[41]

These post-marketing reactions reveal a consistent pattern of autoimmune, neurological and other chronic disorders that would appear or only be diagnosed years after vaccinating a baby. Nevertheless, … HHS responds to these post-marketing reports of chronic life-long injuries by saying that "causation has not been proven," knowing … that causation is highly unlikely to be proven, one way or another, until a placebo-controlled trial of sufficient duration is conducted.

By approving, recommending and aggressively promoting use of the Hepatitis B vaccine for all infants, HHS created a liability-free captive market for Merck and GSK by ensuring millions of babies every year will be injected with their Hepatitis B products. Since HHS's recommendation in 1991 for the universal pediatric use of these products, these companies have generated over $10 billion in

[40] *See* n. 17, *supra.*

[41] *Id*.

> sales from this vaccine. Yet, HHS's response makes clear that it lacked the clinical trial safety data necessary to support its licensure and aggressive marketing of this product for use in all babies.
>
> It is deeply troubling that, despite repeated assurances by HHS that the safety science for this vaccine is robust and complete, when we demanded to actually see this science, HHS was unable to produce it because it apparently does not exist. …
>
> Please identify and provide a copy of any placebo-controlled trial with a safety review period longer than one week that HHS relied upon when it recommended that every baby in this country receive either Recombivax HB or Engerix-B on the first day of life.[42]

11. HHS has not responded or provided any information in response to the foregoing request. No response was received even after ICAN sent a follow-up letter to HHS, dated March 10, 2020, stating that "It has now been over 13 months since ICAN submitted these follow-up questions and concerns regarding vaccine safety. Nonetheless, HHS has failed to respond to the questions posed in our letter of December 31, 2018, nor to any of the substance in that letter."[43]

12. In the summer of 2019, ICAN submitted FOIA requests directly to the FDA requesting the clinical trials relied upon by the FDA to license Engerix-B and Recombivax HB which reviewed safety for more than one week after administration.[44] The FDA has failed to produce any such clinical trials. In sum, neither the FDA nor HHS, despite repeated demands, have been able to produce any clinical trials that would support the safety of these products such that the FDA could have fulfilled its statutory duty to ensure their safety prior to licensing them for injection into newborns, infants and toddlers.

C. Environmental Impact

13. ICAN hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

D. Economic Impact

14. Economic impact information will be submitted upon request of the commissioner.

---

[42] *See* n. 25, *supra*.

[43] https://www.icandecide.org/wp-content/uploads/2020/08/ICAN-Follow-Up-Final.pdf (last visited Sept. 3, 2020).

[44] https://www.icandecide.org/wp-content/uploads/2020/08/Binder1.pdf (last visited Sept. 3, 2020).

E. Certification

15. The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

16. ICAN therefore respectfully urges that the action requested above be adopted forthwith.

Respectfully submitted,

/s/ Aaron Siri
Aaron Siri
Elizabeth Brehm
Jessica Wallace
SIRI & GLIMSTAD LLP
200 Park Avenue
17th Floor
New York, NY 10166
Telephone: (212) 532-1091
Facsimile: (646) 417-5967
Email: aaron@sirillp.com

Footnote 4

Centers for Disease Control and Prevention

Immunization Schedules

Table 1. Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

Always make recommendations by determining needed vaccines based on age (Table 1), determining appropriate intervals for catch-up, if needed (Table 2), assessing for medical indications (Table 3), and reviewing special situations (Notes).

Get Email Updates

Table 1. By age | Table 2. Catch-up schedule | Table 3. By medical indications | Schedule Changes & Guidance | Parent-friendly schedule | Resources for health care

- 8.5″x11″ print color [8 pages]
- 8.5″x11″ print black and white [8 pages]
- Compliant version of this schedule

- Vaccines in the Child and Adolescent Immunization Schedule
- Learn how to display current schedules from your website.

Download Schedules App

Legend

Range of recommended ages for all children	Range of recommended ages for catch-up immunization	Range of recommended ages for certain high-risk groups	Recommended based on shared clinical decision-making or *can be used in this age group	No recommendation/Not applicable

Birth to 15 Months

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos
Hepatitis B (HepB)	1st dose	2nd dose			←3rd dose→			
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See notes			
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			←4th dose→
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See notes		←3rd or 4th dose, See notes→	
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		←4th dose→	
Inactivated poliovirus (IPV: <18 yrs)			1st dose	2nd dose	←3rd dose→			

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos
Influenza (IIV)					Annual vaccination 1 or 2 doses			
or Influenza (LAIV)								
Measles, mumps, rubella (MMR)					See notes		←1st dose→	
Varicella (VAR)							←1st dose→	
Hepatitis A (HepA)					See notes		←2-dose series, See notes→	
Tetanus, diphtheria, & acellular pertussis (Tdap: ≥7 yrs)								
Human papillomavirus (HPV)								
Meningococcal (MenACWY-D: ≥9 mos; MenACWY-CRM: ≥2 mos)			See notes					
Meningococcal B (MenB)								
Pneumococcal polysaccharide (PPSV23)								

18 Months to 18 Years

Vaccines	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Hepatitis B (HepB)	←3rd dose→								
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)									
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)	←4th dose→			5th dose					
Haemophilus influenzae type b (Hib)									
Pneumococcal conjugate (PCV13)									

Vaccines	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Inactivated poliovirus (IPV: <18 yrs)	←3rd dose→			4th dose					
Influenza (IIV)	Annual vaccination 1 or 2 doses					Annual vaccination 1 dose only			
or Influenza (LAIV)			Annual vaccination 1 or 2 doses		or	Annual vaccination 1 dose only			
Measles, mumps, rubella (MMR)				2nd dose					
Varicella (VAR)				2nd dose					
Hepatitis A (HepA)	← 2-dose series, See notes→								
Tetanus, diphtheria, & acellular pertussis (Tdap: ≥7 yrs)						Tdap			
Human papillomavirus (HPV)					*	See notes			
Meningococcal (MenACWY-D: ≥9 mos; MenACWY-CRM: ≥2 mos)	See notes					1st dose		2nd dose	
Meningococcal B (MenB)						See notes			
Pneumococcal polysaccharide (PPSV23)			See notes						

Administer recommended vaccines if immunization history is incomplete or unknown. Do not restart or add doses to vaccine series for extended intervals between doses. When a vaccine is not administered at the recommended age, administer at a subsequent visit. The use of trade names is for identification purposes only and does not imply endorsement by the ACIP or CDC.

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

For vaccine recommendations for persons 19 years of age or older, see the Recommended Adult Immunization Schedule.

Additional information

- Consult relevant ACIP statements for detailed recommendations.

- For information on contraindications and precautions for the use of a vaccine, consult the General Best Practice Guidelines for Immunization and relevant ACIP statements.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in General Best Practice Guidelines for Immunization.
- Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in General Best Practice Guidelines for Immunization, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics, 2018:67–111).
- For information regarding vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html .

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix or Quadracel])

Routine vaccination

- 5-dose series at 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently administered as early as 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
- For other catch-up guidance, see Table 2.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB, Hiberix, or Pentacel:** 4-dose series at 2, 4, 6, 12–15 months
- **PedvaxHIB:** 3-dose series at 2, 4, 12–15 months

Catch-up vaccination

- **Dose 1 at 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before 12 months and dose 2 before 15 months:** Administer dose 3 (final dose) 8 weeks after dose 2.
- **2 doses of PedvaxHIB before 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **Unvaccinated at 15–59 months:** 1 dose

- Unvaccinated at 15–59 months: 1 dose
- **Previously unvaccinated children age 60 months or older** who are not considered high risk do not require catch-up vaccination.
- For other catch-up guidance, see Table 2.

Special situations

- **Chemotherapy or radiation treatment:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

*Unvaccinated = Less than routine series (through 14 months) OR no doses (15 months or older)

Hepatitis A vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series (minimum interval: 6 months) beginning at age 12 months

Catch-up vaccination

- Unvaccinated persons through 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).

International travel

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A:

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A:
  - **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between 12 and 23 months of age
  - **Unvaccinated age 12 months and older:** Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination (minimum age: birth)

Birth dose (monovalent HepB vaccine only)

- **Mother is HBsAg-negative:** 1 dose within 24 hours of birth for **all** medically stable infants ≥2,000 grams. Infants <2,000 grams: administer 1 dose at chronological age 1 month or hospital discharge.
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **HBIG** in addition to HepB vaccine (in separate limbs) within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series

- 3-dose series at 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination

- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB** only).
- Adolescents 18 years and older may receive a 2-dose series of HepB (**Heplisav-B®**) at least 4 weeks apart.
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).
- For other catch-up guidance, see Table 2.

Special situations

- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Revaccination** may be recommended for certain populations, including:
  - **Infants born to HBsAg-positive mothers**
  - **Hemodialysis patients**
  - **Other immunocompromised persons**
- For detailed revaccination recommendations, please see the HepB *MMWR* publications.

Human papillomavirus vaccination (minimum age: 9 years)

Routine and catch-up vaccination

- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9 through 14 years at initial vaccination:** 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- If completed valid vaccination series with any HPV vaccine, no additional doses needed

Special situations

- **Immunocompromising conditions, including HIV infection:** 3-dose series as above
- **History of sexual abuse or assault:** Start at age 9 years
- **Pregnancy:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Influenza vaccination (minimum age: 6 months [IIV], 2 years [LAIV], 18 years [recombinant influenza vaccine, RIV])

Routine vaccination

- Use any influenza vaccine appropriate for age and health status annually:
  - 2 doses, separated by at least 4 weeks, for **children age 6 months–8 years** who have received fewer than 2 influenza vaccine doses before July 1, 2019, or whose influenza vaccination history is unknown (administer dose 2 even if the child turns 9 between receipt of dose 1 and dose 2)
  - 1 dose for **children age 6 months–8 years** who have received at least 2 influenza vaccine doses before July 1, 2019
  - 1 dose for **all persons age 9 years and older**
- For the 2020–21 season, see the 2020–21 ACIP influenza vaccine recommendations.

Special situations

- **Egg allergy, hives only**: Any influenza vaccine appropriate for age and health status annually
- **Egg allergy with symptoms other than hives** (e.g., angioedema, respiratory distress, need for emergency medical services or epinephrine): Any influenza vaccine appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions
- **LAIV should not be used** in persons with the following conditions or situations:
  - History of severe allergic reaction to a previous dose of any influenza vaccine or to any vaccine component (excluding egg, see details above)
  - Receiving aspirin or salicylate-containing medications
  - Age 2–4 years with history of asthma or wheezing
  - Immunocompromised due to any cause (including medications and HIV infection)
  - Anatomic or functional asplenia
  - Cochlear implant
  - Cerebrospinal fluid-oropharyngeal communication
  - Close contacts or caregivers of severely immunosuppressed persons who require a protected environment
  - Pregnancy
  - Received influenza antiviral medications within the previous 48 hours

Measles, mumps, and rubella vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 4 weeks after dose 1.

Catch-up vaccination

- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart
- The maximum age for use of MMRV is 12 years.

Special situations

International travel

- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series with dose 1 at 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months and older:** 2-dose series at least 4 weeks apart before departure

Meningococcal serogroup A,C,W,Y vaccination (minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra])

Routine vaccination

- 2-dose series at 11–12 years, 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Menveo**
  - Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency or complement inhibitor use:**
    - Age 9–23 months: 2-dose series at least 12 weeks apart
    - Age 24 months or older: 2-dose series at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - Age 9–23 months: Not recommended
    - Age 24 months or older: 2-dose series at least 8 weeks apart
    - **Menactra** must be administered at least 4 weeks after completion of PCV13 series.

Travel in countries **with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj:**

- Children less than age 24 months:
  - **Menveo (age 2–23 months):**
    - Dose 1 at 8 weeks: 4-dose series at 2, 4, 6, 12 months
    - Dose 1 at 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)

        - Dose 1 at 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
    - **Menactra (age 9–23 months):**
        - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose **Menveo** or **Menactra**

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo** or **Menactra**

Adolescent vaccination of children who received MenACWY prior to age 10 years:

- **Children for whom boosters are recommended** because of an ongoing increased risk of meningococcal disease (e.g., those with complement deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk (see below).
- **Children for whom boosters are not recommended** (e.g., those who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose 1 at age 11–12 years and dose 2 at age 16 years.

Note: Menactra should be administered either before or at the same time as DTaP. For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and for additional meningococcal vaccination information, see meningococcal *MMWR* publications.

Meningococcal serogroup B vaccination (minimum age: 10 years [MenB-4C, Bexsero; MenB-FHbp, Trumenba])

Shared Clinical Decision-Making

- **Adolescents not at increased risk** age 16–23 years (preferred age 16–18 years) based on shared clinical decision-making:
    - **Bexsero:** 2-dose series at least 1 month apart
    - **Trumenba:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 3-dose series at 0, 1–2, 6 months

Bexsero and **Trumenba** are not interchangeable; the same product should be used for all doses in a series. For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and for additional meningococcal vaccination information, see ACIP Recommendations.

Pneumococcal vaccination (minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13

- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13

- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series

- For other catch-up guidance, see Table 2.

Special situations

High-risk conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during the same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma treated with high-dose, oral corticosteroids), diabetes mellitus:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a 2nd dose of PPSV23 5 years later

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a 2nd dose of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

Chronic liver disease, alcoholism:

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

*Incomplete series = Not having received all doses in either the recommended series or an age-appropriate catch-up series. See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations [24 pages] for complete schedule details.

Poliovirus vaccination (minimum age: 6 weeks)

Routine vaccination

- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose at or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended at or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination

- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents 18 years and older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See Guidance for Assessment of Poliovirus Vaccination Status and Vaccination of Children Who Have Received Poliovirus Vaccine Outside the United States.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.
  - Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).
  - Doses of OPV administered on or after April 1, 2016, should not be counted.
  - For guidance to assess doses documented as "OPV," see Errata: Vol. 66, No. 1.
- For other catch-up guidance, see Table 2.

Rotavirus vaccination (minimum age: 6 weeks)

Routine vaccination

- **Rotarix:** 2-dose series at 2 and 4 months
- **RotaTeq:** 3-dose series at 2, 4, and 6 months
- If any dose in the series is either **RotaTeq** or unknown, default to 3-dose series.

Catch-up vaccination

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination (minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination

- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination

- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td or Tdap booster every 10 years
- **Persons age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- **Tdap administered at 7–10 years**
  - **Children age 7–9 years** who receive Tdap should receive the routine Tdap dose at age 11–12 years.
  - **Children age 10 years** who receive Tdap do not need to receive the routine Tdap dose at age 11–12 years.
- **DTaP inadvertently administered at or after age 7 years:**
  - **Children age 7–9 years:** DTaP may count as part of catch-up series. Routine Tdap dose at age 11–12 years should be administered.
  - **Children age 10–18 years:** Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Table 2.
- For information on use of Tdap or Td as tetanus prophylaxis in wound management, see Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP).

*Fully vaccinated = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older.

Varicella vaccination (minimum age: 12 months)

Routine vaccination

- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 3 months after dose 1 (a dose administered after a 4-week interval may be counted).

Catch-up vaccination

- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* [48 pages]) have 2-dose series:
  - **Age 7–12 years:** routine interval: 3 months (a dose administered after a 4-week interval may be counted)
  - **Age 13 years and older:** routine interval: 4–8 weeks (minimum interval: 4 weeks)
  - The maximum age for use of MMRV is 12 years.

Vaccines in the Child and Adolescent Immunization Schedule

Vaccines	Abbreviations	Trade Names
Diphtheria, tetanus, and acellular pertussis vaccine	DTaP	Daptacel® Infanrix®
Diphtheria, tetanus vaccine	DT	No Trade Name
Haemophilus influenzae type B vaccine	Hib (PRP-T) Hib (PRP-OMP)	ActHIB® Hiberix® PedvaxHIB®
Hepatitis A vaccine	HepA	Havrix® Vaqta®
Hepatitis B vaccine	HepB	Engerix-B® Recombivax HB®

Vaccines	Abbreviations	Trade Names
Human papillomavirus vaccine	HPV	Gardasil 9®
Influenza vaccine (inactivated)	IIV	Multiple
Influenza vaccine (live, attenuated)	LAIV	FluMist® Quadrivalent
Measles, mumps, and rubella vaccine	MMR	M-M-R® II
Meningococcal serogroups A, C, W, Y vaccine	MenACWY-D MenACWY-CRM	Menactra® Menveo®
Meningococcal serogroup B vaccine	MenB-4C MenB-FHbp	Bexsero® Trumenba®
Pneumococcal 13-valent conjugate vaccine	PCV13	Prevnar 13®
Pneumococcal 23-valent polysaccharide vaccine	PPSV23	Pneumovax® 23
Poliovirus vaccine (inactivated)	IPV	IPOL®
Rotavirus vaccine	RV1 RV5	Rotarix® RotaTeq®
Tetanus, diphtheria, and acellular pertussis vaccine	Tdap	Adacel® Boostrix®
Tetanus and diphtheria vaccine	Td	Tenivac® TDvax™
Varicella vaccine	VAR	Varivax®

Combination Vaccines

(Use combination vaccines instead of separate injections when appropriate)

Vaccines	Abbreviations	Trade Names
DTaP, hepatitis B, and inactivated poliovirus vaccine	DTaP-HepB-IPV	Pediarix®
DTaP, inactivated poliovirus, and *Haemophilus influenzae* type B vaccine	DTaP-IPV/Hib	Pentacel®
DTaP and inactivated poliovirus vaccine	DTaP-IPV	Kinrix® Quadracel®
Measles, mumps, rubella, and varicella vaccines	MMRV	ProQuad®

This schedule is recommended by the Advisory Committee on Immunization Practices (ACIP) and approved by the Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), and American College of Nurse-Midwives (ACNM).

The comprehensive summary of the ACIP recommended changes made to the child and adolescent immunization schedule can be found in the February 6, 2020 *MMWR*.

Report

- Suspected cases of reportable vaccine-preventable diseases or outbreaks to your state or local health department
- Clinically significant adverse events to the Vaccine Adverse Event Reporting System (VAERS) at www.vaers.hhs.gov or (800-822-7967)

Helpful information

- Complete ACIP recommendations
- General Best Practice Guidelines for Immunization
- Outbreak information (including case identification and outbreak response), see Manual for the Surveillance of Vaccine-Preventable Diseases

Page last reviewed: February 3, 2020

MMWR

Recommendations and Reports

November 22, 1991 / 40(RR-13);1-19

Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States Through Universal Childhood Vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP)

Immunization Practices Advisory Committee

Membership List, September 1991

CHAIRMAN EX OFFICIO MEMBERS

Samuel L. Katz, M.D. John La Montagne, Ph.D. Duke University Medical Center National Institutes of Health

EXECUTIVE SECRETARY Carolyn Hardegree, M.D.

Food and Drug Administration Claire V. Broome, M.D. Centers for Disease Control LIAISON REPRESENTATIVES

MEMBERS American Academy of Family Physicians

Ronald C. Van Buren, M.D.

- Stanley E. Broadnax, M.D. Columbus, Ohio Cincinnati Health Department

American Academy of Pediatrics

- James D. Cherry, M.D. Georges Peter, M.D. University of California School Providence, Rhode Island

of Medicine (Los Angeles)

Caroline B. Hall, M.D. Mary Lou Clements, M.D. Rochester, New York Johns Hopkins University (Baltimore, Maryland) American College of Physicians

Pierce Gardner, M.D. David W. Fraser, M.D. Stonybrook, New York Swarthmore College (Pennsylvania) American Hospital Association

William Schaffner, M.D.

- Caroline B. Hall, M.D. Nashville, Tennessee University of Rochester

School of Medicine and American Medical Association

Dentistry (New York) Edward A. Mortimer, Jr., M.D.

Cleveland, Ohio Carlos E. Hernandez, M.D. Kentucky Department for Canadian National Advisory Committee

Health Services on Immunization

Susan E. Tamblyn, M.D., Dr. P.H. Gregory R. Istre, M.D. Stratford, Ontario Medical City Hospital Canada (Dallas, Texas)

Department of Defense Carlos H. Ramirez-Ronda, M.D. Michael Peterson, D.V.M. University of Puerto Rico M.P.H., Dr. P.H.

School of Medicine (San Juan) Washington, D.C.

Mary E. Wilson, M.D. National Vaccine Program Mount Auburn Hospital Kenneth J. Bart, M.D. (Cambridge, Massachusetts) Rockville, Maryland

- Terms expired 6/30/91.

The following statement updates all previous recommendations on protection against hepatitis B virus infection, including use of hepatitis B vaccine and hepatitis B immune globulin for prophylaxis against hepatitis B virus infection (MMWR 1985;34:313-24, 329-35, MMWR 1987;36:353-66, and MMWR 1990;39{No. RR-2}:8-19) and universal screening of pregnant women to prevent perinatal hepatitis B virus transmission (MMWR 1988;37:341-46, 51, and MMWR 1990;39{No. RR-2}:8-19). Recommendations concerning the prevention of other types of viral hepatitis are found in MMWR 1990;39(No. RR-2): 1-8, 22-26.

This document provides the rationale for a comprehensive strategy to eliminate transmission of hepatitis B virus in the United States. This prevention strategy includes making hepatitis B vaccine a part of routine vaccination schedules for all infants.

INTRODUCTION

The acute and chronic consequences of hepatitis B virus (HBV) infection are major health problems in the United States. The reported incidence of acute hepatitis B increased by 37% from 1979 to 1989, and an estimated 200,000-300,000 new infections occurred annually during the period 1980- 1991. The estimated 1 million-1.25 million persons with chronic HBV infection in the United States are potentially infectious to others. In addition, many chronically infected persons are at risk of long-term sequelae, such as chronic liver disease and primary hepatocellular carcinoma; each year approximately 4,000-5,000 of these persons die from chronic liver disease (1).

Immunization with hepatitis B vaccine is the most effective means of preventing HBV infection and its consequences. In the United States, most infections occur among adults and adolescents (2,3). The recommended strategy for preventing these infections has been the selective vaccination of persons with

identified risk factors (1,2). However, this strategy has not lowered the incidence of hepatitis B, primarily because vaccinating persons engaged in high-risk behaviors, life-styles, or occupations before they become infected generally has not been feasible. In addition, many infected persons have no identifiable source for their infections and thus cannot be targeted for vaccination (2).

Preventing HBV transmission during early childhood is important because of the high likelihood of chronic HBV infection and chronic liver disease that occurs when children less than 5 years of age become infected (3). Testing to identify pregnant women who are hepatitis B surface antigen (HBsAg)-positive and providing their infants with immunoprophylaxis effec- tively prevents HBV transmission during the perinatal period (4,5). Integrating hepatitis B vaccine into childhood vaccination schedules in populations with high rates of childhood infection (e.g., Alaskan Natives and Pacific Islanders) has been shown to interrupt HBV transmission (6).

This document provides the rationale for a comprehensive strategy to eliminate transmission of HBV and ultimately reduce the incidence of hepatitis B and hepatitis B-associated chronic liver disease in the United States. The recommendations for implementing this strategy include making hepatitis B vaccine a part of routine vaccination schedules for infants.

EPIDEMIOLOGY AND PREVENTION OF HEPATITIS B VIRUS INFECTION

Infections among Infants and Children

In the United States, children become infected with HBV through a variety of means. The risk of perinatal HBV infection among infants born to HBV-infected mothers ranges from 10% to 85%, depending on each mother's hepatitis B e antigen (HBeAg) status (3,7,8). Infants who become infected by perinatal transmission have a 90% risk of chronic infection, and up to 25% will die of chronic liver disease as adults (9). Even when not infected during the perinatal period, children of HBV-infected mothers remain at high risk of acquiring chronic HBV infection by person-to-person (horizontal) transmission during the first 5 years of life (10). More than 90% of these infections can be prevented if HBsAg-positive mothers are identified so that their infants can receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) soon after birth (4,5).

Because screening selected pregnant women for HBsAg has failed to identify a high proportion of HBV-infected mothers (11,12), prenatal HBsAg testing of all pregnant women is now recommended (1,13,14). Universal prenatal testing would identify an estimated 22,000 HBsAg-positive women and could prevent at least 6,000 chronic HBV infections annually (3). Screening and vaccination programs for women and infants receiving care in the public sector have already been initiated through state immunization projects.

Horizontal transmission of HBV during the first 5 years of life occurs frequently in populations in which HBV infection is endemic. The risk of chronic infection is age dependent, ranging from 30% to 60% for children 1-5 years of age (15). Worldwide, it has been recommended that, in popula- tions in which HBV infection is acquired during childhood, hepatitis B vaccine should be integrated into routine vaccination schedules for infants, usually as a part of the World Health Organization's Expanded Programme on Immunization (16). In the United States, racial/ethnic groups shown to have high rates of childhood HBV infection include Alaskan Natives (6,17), Pacific Islanders (18), and infants of first-generation immigrant mothers from parts of the world where HBV infection is endemic, especially Asia (19,20). Vaccination programs to prevent perinatal, childhood, and adult HBV infections among Alaskan Natives were begun in late 1982; as a result, the incidence of acute hepatitis B in this population has declined by over 99% (6). Hepatitis B vaccine was integrated into vaccination schedules for infants in American Samoa beginning in 1986 and by 1990 was incorporated into the schedules of the remaining Pacific Islands under U.S. jurisdiction.

Each year, approximately 150,000 infants are born to women who have immigrated to the United States from areas of the world where HBV infection is highly endemic (3). Children born to HBsAg-positive mothers can be identified through prenatal screening programs. However, children born to HBsAg-

negative immigrant mothers are still at high risk of acquiring HBV infection, usually from other HBV carriers in their families or communities (3,19,20). Infections among these children can be prevented by making hepatitis B vaccine part of their routine infant vaccinations (1).

Infections among Adolescents and Adults

In the United States most persons with hepatitis B acquire the infection as adolescents or adults. Several specific modes of transmission have been identified, including sexual contact, especially among homosexual men and persons with multiple heterosexual partners; parenteral drug use; occupational exposures; household contact with a person who has an acute infection or with a chronic carrier; receipt of certain blood products; and hemodialysis. However, over one-third of patients with acute hepatitis B do not have readily identifiable risk factors (1,2).

The rates of HBV infection differ significantly among various racial and ethnic groups (2,21). For example, the prevalence of infection among adolescents and adults has been shown to be threefold to fourfold greater for blacks than for whites and to be associated with serologic evidence of previous infection with syphilis (21,22).

Efforts to vaccinate persons in the major risk groups have had limited success. For example, programs directed at injecting drug users failed to motivate them to receive three doses of vaccine (CDC, unpublished data). Health-care providers are often not aware of groups at high risk of HBV infection and frequently do not identify candidates for vaccination during routine health-care visits (CDC, unpublished data). In addition, there has been limited vaccination of susceptible household and sexual contacts of HBsAg carriers identified in screening programs for blood donors (23). Hepatitis B vaccination of health-care workers appears to have resulted in a substantial decrease in the rate of disease in this group, but has had little effect on overall rates of hepatitis B (2). Moreover, to achieve widespread vaccination of persons at occupational risk, regulations have had to be developed to ensure implementation of vaccination programs (24).

Educational programs to reduce parenteral drug use and unprotected sexual activity are important components of the strategy to prevent infection with the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome. These programs appear to have reduced the risk of HBV infections among homosexual men but have not had an impact on hepatitis B attributable to parenteral drug use or heterosexual trans- mission (2). Educational efforts alone are not likely to fully eliminate the high-risk behaviors responsible for HBV transmission.

EPIDEMIOLOGY AND PREVENTION OF HEPATITIS DELTA VIRUS INFECTION

Hepatitis delta virus (HDV) is a defective virus that causes infection only in the presence of active HBV infection (25). HDV infection occurs as either coinfection with HBV or superinfection of an HBV carrier. Coinfec- tion usually resolves; superinfection, however, frequently causes chronic HDV infection and chronic active hepatitis. Both types of infection may cause fulminant hepatitis.

Routes of transmission are similar to those of HBV. In the United States, HDV infection most commonly affects persons at high risk of HBV infection, particularly injecting drug users and persons receiving clotting factor concentrates (26). Preventing acute and chronic HBV infection of susceptible persons will also prevent HDV infection.

STRATEGY TO ELIMINATE HEPATITIS B VIRUS TRANSMISSION

A comprehensive strategy to prevent HBV infection, acute hepatitis B, and the sequelae of HBV infection in the United States must eliminate transmission that occurs during infancy and childhood, as well as during adolescence and adulthood. In the United States it has become evident that HBV transmission cannot be prevented through vaccinating only the groups at high risk of infection. No current medical treatment will reliably eliminate chronic HBV infection and thus eliminate the source of new infections in

susceptible persons (27). Therefore, new infections can be prevented only by immunizing susceptible persons with hepatitis B vaccine. Routine visits for prenatal and well-child care can be used to target hepatitis B prevention. A comprehensive prevention strategy includes a) prenatal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for the prevention of perinatal infection and to identify household contacts who should be vaccinated, b) routine vaccin- ation of children born to HBsAg-negative mothers, c) vaccination of certain adolescents, and d) vaccination of adults at high risk of infection.

Infants and children can receive hepatitis B vaccine during routine health-care visits; no additional visits would be required. Costs include that of the vaccine and the incremental expense associated with delivering an additional vaccine during a scheduled health-care visit. Implementation of this immunization strategy would be greatly facilitated by the develop- ment and use of multiple-antigen vaccines (e.g., diphtheria-tetanus- pertussis {DTP}/hepatitis B, Haemophilus influenzae type b conjugate/ hepatitis B). These vaccines would reduce the number of injections received by the infant, reduce the cost of administration, and greatly facilitate widespread vaccine delivery.

Since most HBV infections occur among adults, disease control could be accelerated by vaccinating emerging at-risk populations, such as adoles- cents and susceptible contacts of chronic HBV carriers. The recommendation for universal infant vaccination neither precludes vaccinating adults identified to be at high risk of infection nor alters previous recommen- dations for postexposure prophylaxis for hepatitis B (1).

The reduction in acute hepatitis B and hepatitis B-associated chronic liver disease resulting from universal infant vaccination may not become apparent for a number of years. However, universal HBsAg screening of pregnant women to prevent perinatal HBV infection has been shown to be cost saving (28, CDC, unpublished data), and the estimated cost of universal hepatitis B vaccination for infants is less than the direct medical and work-loss costs associated with the estimated 5% lifetime risk of infection (CDC, unpublished data). Currently, the cost of an infant's dose of hepatitis B vaccine delivered in the public sector is about the same as each of the other childhood vaccinations. Vaccinating adolescents and adults is substantially more expensive because of the higher vaccine cost and the higher implementation costs of delivering vaccine to target populations. In the long term, universal infant vaccination would eliminate the need for vaccinating adolescents and high-risk adults.

PROPHYLAXIS AGAINST HEPATITIS B VIRUS INFECTION

Two types of products are available for prophylaxis against HBV infection. Hepatitis B vaccine, which provides long-term protection against HBV infection, is recommended for both preexposure and postexposure prophylaxis. HBIG provides temporary protection (i.e., 3-6 months) and is indicated only in certain postexposure settings.

Hepatitis B Immune Globulin

HBIG is prepared from plasma known to contain a high titer of antibody against HBsAg (anti-HBs). In the United States, HBIG has an anti-HBs titer of >100,000 by radioimmunoassay. The human plasma from which HBIG is prepared is screened for antibodies to HIV; in addition, the process used to prepare HBIG inactivates and eliminates HIV from the final product. There is no evidence that HIV can be transmitted by HBIG (29,30).

Hepatitis B Vaccine

Two types of hepatitis B vaccine have been licensed in the United States. One, which was manufactured from the plasma of chronically infected persons, is no longer produced in the United States. The currently available vaccines are produced by recombinant DNA technology.

The recombinant vaccines are produced by using HBsAg synthesized by Saccharomyces cerevisiae (common bakers' yeast), into which a plasmid containing the gene for HBsAg has been inserted. Purified HBsAg is obtained by lysing the yeast cells and separating HBsAg from the yeast components by biochemical and biophysical techniques. Hepatitis B vaccines are packaged to contain 10-40 ug of HBsAg protein/mL after adsorption to aluminum hydroxide (0.5 mg/mL); thimerosal (1:20,000 concentration) is added as a preservative.

Routes and sites of administration.

The recommended series of three intramuscular doses of hepatitis B vaccine induces a protective antibody response (anti-HBs >=10 milli-inter- national units {mIU}/mL) in >90% of healthy adults and in >95% of infants, children, and adolescents (31-33). Hepatitis B vaccine should be admin- istered only in the deltoid muscle of adults and children or in the antero- lateral thigh muscle of neonates and infants; the immunogenicity of the vaccine for adults is substantially lower when injections are administered in the buttock (34). When hepatitis B vaccine is administered to infants at the same time as other vaccines, separate sites in the anterolateral thigh may be used for the multiple injections. This method is preferable to administering vaccine at sites such as the buttock or deltoid.

Compared with three standard doses admistered intramuscularly, three low doses of plasma-derived or recombinant vaccine administered intra- dermally to adults result in lower seroconversion rates (55%-81%) and lower final titers of anti-HBs (35-38), although four doses of plasma-derived vaccine administered intradermally have produced responses comparable with vaccine administered intramuscularly (39). Plasma-derived vaccine admin- istered intradermally to infants and children does not induce an adequate antibody response (40). At this time, low-dose intradermal vaccination of adults should be performed only under research protocol with written informed consent. Persons who have been vaccinated intradermally should be tested for anti-HBs. Those with an inadequate response (anti-HBs <10 mIU/ mL) should be revaccinated with three full doses of vaccine administered intramuscularly. Intradermal vaccination should not be used for infants or children.

Vaccination during pregnancy.

On the basis of limited experience, there is no apparent risk of adverse effects to developing fetuses when hepatitis B vaccine is admin- istered to pregnant women (CDC, unpublished data). The vaccine contains noninfectious HBsAg particles and should cause no risk to the fetus. HBV infection affecting a pregnant woman may result in severe disease for the mother and chronic infection for the newborn. Therefore, neither pregnancy nor lactation should be considered a contraindication to vaccination of women.

Vaccine Usage

Preexposure prophylaxis

Vaccination schedule and dose. The vaccination schedule most often used for adults and children has been three intramuscular injections, the second and third administered 1 and 6 months, respectively, after the first. An alternate schedule of four doses has been approved for one vaccine that would allow more rapid induction of immunity. However, for preexposure prophylaxis, there is no clear evidence that this regimen provides greater protection than that obtained with the standard three-dose schedule.

Each vaccine has been evaluated to determine the age-specific dose at which an optimum antibody response is achieved. The recommended dose varies by product and the recipient's age and, for infants, by the mother's HBsAg serologic status (Table_1). In general, the vaccine dose for children and adolescents is 50%-75% lower than that required for adults (Table_1).

Incorporating hepatitis B vaccine into childhood vaccination schedules may require modifications of previously recommended schedules. However, a protective level of anti-HBs (>=10 mIU/mL) was

achieved when hepatitis B vaccine was administered in a variety of schedules, including those in which vaccination was begun soon after birth (5,8,41).

In a three-dose schedule, increasing the interval between the first and second doses of hepatitis B vaccine has little effect on immunogenicity or final antibody titer. The third dose confers optimal protection, acting as a booster dose. Longer intervals between the last two doses (4-12 months) result in higher final titers of anti-HBs (42,43). Several studies have shown that the currently licensed vaccines produce high rates of serocon- version (>95%) and induce adequate levels of anti-HBs when administered to infants at birth, 2 months, and 6 months of age or at 2 months, 4 months, and 6 months of age (CDC, Merck Sharpe & Dohme, SmithKline Beecham, unpub- lished data). When the vaccine is administered in four doses at 0, 1, 2, and 12 months, the last dose is necessary to ensure the highest final antibody titer.

When hepatitis B vaccine has been administered at the same time as other vaccines, no interference with the antibody response of the other vaccines has been demonstrated (44).

If the vaccination series is interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by an interval of at least 2 months. If only the third dose is delayed, it should be administered when convenient.

The immune response when one or two doses of a vaccine produced by one manufacturer are followed by subsequent doses from a different manufacturer has been shown to be comparable with that resulting from a full course of vaccination with a single vaccine.

Larger vaccine doses or an increased number of doses are required to induce protective antibody in a high proportion of hemodialysis patients (45,46) and may also be necessary for other immunocompromised persons (e.g., those who take immunosuppressive drugs or who are HIV positive), although few data are available concerning response to higher doses of vaccine by these patients (47).

Prevaccination testing for susceptibility. Susceptibility testing is not indicated for immunization programs for children or for most adoles- cents because of the low rate of HBV infection and the relatively low cost of vaccine. For adults, the decision to do prevaccination testing should include an analysis of cost effectiveness because of the higher cost of the vaccine. Testing for prior infection should be considered for adults in risk groups with high rates of HBV infection (e.g., injecting drug users, homosexual men, and household contacts of HBV carriers). The decision for testing should be based on whether the costs of testing balance the costs of vaccine saved by not vaccinating already-infected persons. Estimates of the cost effectiveness of testing depend on three variables: the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune persons. If susceptibility testing is being considered, careful attention should also be given to the likelihood of patient follow-up and vaccine delivery.

For routine testing, only one antibody test is necessary (antibody either to the core antigen {anti-HBc} or anti-HBs). Anti-HBc testing identifies all previously infected persons, including HBV carriers, but does not differentiate carriers and non-carriers. The presence of anti-HBs identifies previously infected persons, except for HBV carriers. Neither test has a particular advantage for groups expected to have HBV carrier rates <2%, such as health-care workers. Anti-HBc may be preferable so that unnecessary vaccination of HBV carriers can be avoided in groups with high carrier rates.

Postvaccination testing for serologic response. Such testing is not necessary after routine vaccination of infants, children, or adolescents. Testing for immunity is advised only for persons whose subsequent clinical management depends on knowledge of their immune status (e.g., infants born to HBsAg-positive mothers, dialysis patients and staff, and persons with HIV infection). Postvaccination testing should also be considered for persons at occupational risk who may have exposures from injuries with sharp instruments, because knowledge of their antibody response will aid in determining appropriate postexposure prophylaxis. When necessary, postvac- cination testing should be performed from 1 to 6 months after completion of the vaccine series. Testing after immunoprophylaxis of infants born to

HBsAg-positive mothers should be performed from 3 to 9 months after the completion of the vaccination series (see section on Postexposure prophylaxis).

Revaccination of nonresponders. When persons who do not respond to the primary vaccine series are revaccinated, 15%-25% produce an adequate antibody response after one additional dose and 30%-50% after three additional doses (48). Therefore, revaccination with one or more additional doses should be considered for persons who do not respond to vaccination initially.

Postexposure prophylaxis

After a person has been exposed to HBV, appropriate immunoprophylactic treatment can effectively prevent infection. The mainstay of postexposure immunoprophylaxis is hepatitis B vaccine, but in some settings the addition of HBIG will provide some increase in protection. Table_2 provides a guide to recommended treatment for various HBV exposures.

Transmission of perinatal HBV infection can be effectively prevented if the HBsAg-positive mother is identified and if her infant receives appro- priate immunoprophylaxis. Hepatitis B vaccination and one dose of HBIG, administered within 24 hours after birth, are 85%-95% effective in preventing both HBV infection and the chronic carrier state (4,5,8). Hepatitis B vaccine administered alone in either a three-dose or four-dose schedule (Table_1), beginning within 24 hours after birth, is 70%-95% effective in preventing perinatal HBV infections (8,41). The infants of women admitted for delivery who have not had prenatal HBsAg testing pose problems in clinical management. Initiating hepatitis B vaccination at birth for infants born to these women will provide adequate postexposure prophylaxis if the mothers are indeed HBsAg positive. The few infections not prevented by either of these treatment regimens were most likely acquired in utero or may be due to very high levels of maternal HBV-DNA (49).

Serologic testing of infants who receive immunoprophylaxis to prevent perinatal infection should be considered as an aid in the long-term medical management of the few infants who become HBV carriers. Testing for anti-HBs and HBsAg at 9-15 months of age will determine the success of the therapy and, in the case of failure, will identify HBV carriers or infants who may require revaccination.

Recommendations for postexposure prophylaxis in circumstances other than the perinatal period (Table_2) have been addressed in a previous statement and are reprinted as Appendix A to this document.

Vaccine Efficacy and Booster Doses

Clinical trials of the hepatitis B vaccines licensed in the United States have shown that they are 80%-95% effective in preventing HBV infection and clinical hepatitis among susceptible children and adults (5,33,41,50). If a protective antibody response develops after vaccination, vaccine recipients are virtually 100% protected against clinical illness.

The duration of vaccine-induced immunity has been evaluated in long- term follow-up studies of both adults and children (48,51). Only the plasma-derived hepatitis B vaccine has been evaluated because it has had the longest clinical use; however, on the basis of comparable immunogen- icity and short-term efficacy, similar results would be expected with recombinant vaccines. The magnitude of the antibody response induced by the primary vaccination series is predictive of antibody persistence, and a logarithmic decline of antibody levels occurs over time. Among young adults (homosexual men and Alaskan Eskimos) who initially responded to a three- dose vaccine series, loss of detectable antibody has ranged from 13% to 60% after 9 years of follow-up. For children vaccinated after the first year of life, the rate of antibody decline has been lower than for adults (51). The peak antibody titers for infants are lower than those for children immunized after 12 months of age, but the rate of antibody decline is comparable with that observed for adults in the same population.

Long-term studies of healthy adults and children indicate that immuno- logic memory remains intact for at least 9 years and confers protection against chronic HBV infection, even though anti-HBs levels may

become low or decline below detectable levels (48,51,52). In these studies, the HBV infections were detected by the presence of anti-HBc. No episodes of clinical hepatitis were reported and HBsAg was not detected, although brief episodes of viremia may not have been detected because of infrequent testing. The mild, inapparent infections among persons who have been previously vaccinated should not produce the sequelae associated with chronic HBV infection and should provide lasting immunity. In general, follow-up studies of children vaccinated at birth to prevent perinatal HBV infection have shown that a continued high level of protection from chronic HBV infections persists at least 5 years (52,53).

For children and adults whose immune status is normal, booster doses of vaccine are not recommended, nor is serologic testing to assess antibody levels necessary. The possible need for booster doses will be assessed as additional information becomes available. For hemodialysis patients, vaccine-induced protection may be less complete and may persist only as long as antibody levels are >=10 mIU/mL. For these patients, the need for booster doses should be assessed by annual antibody testing, and a booster dose should be administered when antibody levels decline to <10 mIU/mL.

Vaccine Side Effects and Adverse Reactions

Hepatitis B vaccines have been shown to be safe when administered to both adults and children. Over 4 million adults have been vaccinated in the United States, and at least that many children have received hepatitis B vaccine worldwide.

Vaccine-associated side effects

Pain at the injection site (3%-29%) and a temperature greater than 37.7 C (1%-6%) have been among the most frequently reported side effects among adults and children receiving vaccine (5,31-33,50). In placebo-controlled studies, these side effects were reported no more frequently among vaccinees than among persons receiving a placebo (33,50). Among children receiving both hepatitis B vaccine and DTP vaccine, these mild side effects have been observed no more frequently than among children receiving DTP vaccine alone.

Serious adverse events

In the United States, surveillance of adverse reactions has shown a possible association between Guillain-Barre syndrome (GBS) and receipt of the first dose of plasma-derived hepatitis B vaccine (54, CDC unpublished data). GBS was reported at a very low rate (0.5/100,000 vaccinees), no deaths were reported, and all reported cases were among adults. An estimated 2.5 million adults received one or more doses of recombinant hepatitis B vaccine during the period 1986-1990. Available data from reporting systems for adverse events do not indicate an association between receipt of recombinant vaccine and GBS (CDC, unpublished data).

Until recently, large-scale hepatitis B vaccination programs for infants (e.g., Taiwan, Alaska, and New Zealand) have primarily used plasma- derived hepatitis B vaccine. No association has been found between vaccin- ation and the occurrence of severe adverse events, including seizures and GBS (55, B. McMahon and A. Milne, unpublished data). However, systematic surveillance for adverse reactions has been limited in these populations, and only a small number of children have received recombinant vaccine. Any presumed risk of adverse events possibly associated with hepatitis B vaccination must be balanced against the expected risk of acute and chronic liver disease associated with the current 5% lifetime risk of HBV infection in the United States. It is estimated that, for each U.S. birth cohort, 2,000-5,000 persons will die from HBV-related liver disease.

As hepatitis B vaccine is introduced for routine vaccination of infants, surveillance for vaccine-associated adverse events will continue to be an important part of the program in spite of the current record of safety. Any adverse event suspected to be associated with hepatitis B vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS). VAERS forms can be obtained by calling 1-800-822-7967.

RECOMMENDATIONS

Prevention of Perinatal Hepatitis B Virus Infection

1. All pregnant women should be routinely tested for HBsAg during an early prenatal visit in each pregnancy, preferably at the same time other routine prenatal laboratory testing is done. HBsAg testing should be repeated late in the pregnancy for women who are HBsAg negative but who are at high risk of HBV infection (e.g., injecting drug users, those with intercurrent sexually transmitted diseases) or who have had clinically apparent hepatitis. Tests for other HBV markers are not necessary for the purpose of maternal screening. However, HBsAg- positive women identified during screening may have HBV-related liver disease and should be evaluated (56).

2. Infants born to mothers who are HBsAg positive should receive the appropriate doses of hepatitis B vaccine (Table_1) and HBIG (0.5 mL) within 12 hours of birth. Both should be administered by intra- muscular injection. Hepatitis B vaccine should be administered concur- rently with HBIG but at a different site. Subsequent doses of vaccine should be administered according to the recommended schedule (Table_3).

3. Women admitted for delivery who have not had prenatal HBsAg testing should have blood drawn for testing. While test results are pending, the infant should receive hepatitis B vaccine within 12 hours of birth, in a dose appropriate for infants born to HBsAg-positive mothers (Table_1).

    a. If the mother is later found to be HBsAg positive, her infant should receive the additional protection of HBIG as soon as possible and within 7 days of birth, although the efficacy of HBIG administered after 48 hours of age is not known (57). If HBIG has not been administered, it is important that the infant receive the second dose of hepatitis B vaccine at 1 month and not later than 2 months of age because of the high risk of infection. The last dose should be administered at age 6 months (Table_3). *

    b. If the mother is found to be HBsAg negative, her infant should continue to receive hepatitis B vaccine as part of his or her routine vaccinations (Table_3 and Table_4), in the dose appropriate for infants born to HBsAg-negative mothers (Table_1).

4. In populations in which screening pregnant women for HBsAg is not feasible, all infants should receive their first dose of hepatitis B vaccine within 12 hours of birth, their second dose at 1-2 months of age, and their third dose at 6 months of age as a part of their childhood vaccinations and well-child care (Table_3).

5. Household contacts and sex partners of HBsAg-positive women identified through prenatal screening should be vaccinated. The decision to do prevaccination testing of these contacts to determine susceptibility to HBV infection should be made according to the guidelines in the section "Prevaccination testing for susceptibility." Hepatitis B vaccine should be administered at the age-appropriate dose (Table_1) to those determined to be susceptible or judged likely to be susceptible to infection.

Universal Vaccination of Infants Born to HBsAg-Negative Mothers

1. Hepatitis B vaccination is recommended for all infants, regardless of the HBsAg status of the mother. Hepatitis B vaccine should be incor- porated into vaccination schedules for children. The first dose can be administered during the newborn period, preferably before the infant is discharged from the hospital, but no later than when the infant is 2 months of age (Table_4). Because the highest titers of anti-HBs are achieved when the last two doses of vaccine are spaced at least 4 months apart, schedules that achieve this spacing may be preferable (Table_4). However, schedules with 2-month intervals between doses, which conform to schedules for other childhood vaccines, have been shown to produce a good antibody response (Table_4) and may be appropriate in

populations in which it is difficult to ensure that infants will be brought back for all their vaccinations. The develop- ment of combination vaccines containing HBsAg may lead to other schedules that will allow optimal use of combined antigens.

2. Special efforts should be made to ensure that high levels of hepatitis B vaccination are achieved in populations in which HBV infection occurs at high rates among children (Alaskan Natives, Pacific Islanders, and infants of immigrants from countries in which HBV is endemic).

Vaccination of Adolescents

All adolescents at high risk of infection because they are injecting drug users or have multiple sex partners (more than one partner/6 months) should receive hepatitis B vaccine. Widespread use of hepatitis B vaccine is encouraged. Because risk factors are often not identified directly among adolescents, universal hepatitis B vaccination of teenagers should be implemented in communities where injecting drug use, pregnancy among teenagers, and/or sexually transmitted diseases are common. Adolescents can be vaccinated in school-based clinics, community health centers, family planning clinics, clinics for the treatment of sexually transmitted diseases, and special adolescent clinics.

The 0-, 1-, and 6-month schedule is preferred for vaccinating adoles- cents with the age-appropriate dose of vaccine (Table_1). However, the choice of vaccination schedule should take into account the feasibility of delivering three doses of vaccine over a given period of time. The use of alternate schedules (e.g., 0, 2, and 4 months) may be advisable to achieve complete vaccination.

Vaccination of Selected High-Risk Groups

Efforts to vaccinate persons at high risk of HBV infection should follow the vaccine doses shown in Table_1. High-risk groups for whom vaccination is recommended include:

1. Persons with occupational risk. HBV infection is an occupational hazard for health-care workers and for public-safety workers who have exposure to blood in the workplace (24,58). The risk of acquiring HBV infections from occupational exposures depends on the frequency of percutaneous and permucosal exposure to blood or blood-contaminated body fluids. Any health-care or public-safety worker may be at risk for HBV exposure, depending on the tasks he or she performs. Workers who perform tasks involving contact with blood or blood-contaminated body fluid should be vaccinated (24,58, 59). For public-safety workers whose exposure to blood is infrequent, timely postexposure prophylaxis should be considered rather than routine preexposure vaccination.

   For persons in health-care fields, vaccination should be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions, before trainees have their first contact with blood.

2. Clients and staff of institutions for the developmentally disabled. Susceptible clients in institutions for the developmentally disabled, as well as staff who work closely with clients, should be vaccinated. Susceptible clients and staff who live or work in smaller residential settings with known HBV carriers should also receive hepatitis B vaccine. Clients discharged from residential institutions into community programs should be screened for HBsAg so that appropriate measures can be taken to prevent HBV trans- mission. These measures should include both environmental controls and appropriate use of vaccine.

   Staff of nonresidential day-care programs for the develop- mentally disabled (e.g., schools, sheltered workshops) attended by known HBV carriers have a risk of infection comparable with that of health-care workers and therefore should be vaccinated (60). The risk of infection for other clients appears to be lower than the risk for staff. Vaccination of clients in day care programs may be considered. Vaccination of classroom contacts is strongly encouraged if a classmate who is an

HBV carrier behaves aggres- sively or has special medical problems (e.g., exudative dermatitis, open skin lesions) that increase the risk of exposure to his or her blood or serous secretions.

3. Hemodialysis patients. Hepatitis B vaccination is recommended for susceptible hemodialysis patients. Vaccinating patients early in the course of their renal disease is encouraged because patients with uremia who are vaccinated before they require dialysis are more likely to respond to the vaccine (61). Although their serocon- version rates and anti-HBs titers are lower than those of healthy persons, patients who respond to vaccination will be protected from infection, and the need for frequent serologic testing will be reduced (62).

4. Recipients of certain blood products. Patients who receive clotting-factor concentrates have an increased risk of HBV infection and should be vaccinated as soon as their specific clotting disorder is identified. Prevaccination testing is recom- mended for patients who have already received multiple infusions of these products.

5. Household contacts and sex partners of HBV carriers. All household and sexual contacts of persons identified as HBsAg positive should be vaccinated. The decision to do prevaccination testing to determine susceptibility to HBV infection should be made according to the guidelines described earlier in the section "Prevaccination testing for susceptibility." Hepatitis B vaccine should be admin- istered at the age-appropriate dose (Table_1) to those deter- mined to be susceptible or judged likely to be susceptible to infection.

6. Adoptees from countries where HBV infection is endemic. Adopted or fostered orphans or unaccompanied minors from countries where HBV infection is endemic should be screened for HBsAg (3). If the children are HBsAg positive, other family members should be vaccinated (63).

7. International travelers. Vaccination should be considered for persons who plan to spend more than 6 months in areas with high rates of HBV infection and who will have close contact with the local population. Short-term travelers who are likely to have contact with blood (e.g., in a medical setting) or sexual contact with residents of areas with high or intermediate levels of endemic disease should be vaccinated. Vaccination should begin at least 6 months before travel to allow for completion of the full vaccine series, although a partial series will offer some protection. The alternate four-dose schedule (see Table_1) should provide protection if the first three doses can be delivered before departure.

8. Injecting drug users. All injecting drug users who are susceptible to HBV should be vaccinated as soon as their drug use begins. Because of the high rate of HBV infection in this population, prevaccination screening should be considered as outlined in the section "Prevaccination testing for susceptibility." Injecting drug users known to have HIV infection should be tested for anti-HBs response after completion of the vaccine series. Those who do not respond to vaccination should be counseled accordingly.

9. Sexually active homosexual and bisexual men. Susceptible sexually active homosexual and bisexual men should be vaccinated. Because of the high rate of HBV infection in this population, prevaccination screening should be considered as described in the section "Prevac- cination testing for susceptibility." Men known to have HIV infection should be tested for anti-HBs response after completion of the vaccine series. Those who do not respond to vaccination should be counseled accordingly.

10. Sexually active heterosexual men and women. Vaccination is recom- mended for men and women who are diagnosed as having recently acquired other sexually transmitted diseases, for prostitutes, and for persons who have a history of sexual activity with more than one partner in the previous 6 months (2). Most patients seen in clinics for sexually transmitted diseases should be considered candidates for vaccination.

11. Inmates of long-term correctional facilities. Prison officials should consider undertaking screening and vaccination programs directed at inmates with histories of high-risk behaviors.

EVOLVING ISSUES IN HEPATITIS B IMMUNIZATION PROGRAMS

Hepatitis B vaccine has now been used extensively throughout the world and is currently being incorporated into the Expanded Programme on Immuni- zation of the World Health Organization (16). New information, vaccines, and technology will have implications for this effort, and adjustments and changes are expected to occur over the years. Some of the issues that can be expected to be addressed in clinical and operational studies include the following:

1. In most developing countries with hepatitis B immunization programs, the first dose of vaccine is administered to all infants soon after birth to prevent perinatal infections; pregnant women are not screened for HBsAg; and HBIG is not used (8,16,45). The feasibility and effectiveness of incorporating this approach into the hepatitis B prevention strategy for the United States must be evaluated.

2. Booster doses of hepatitis B vaccine have not been recommended because of the persistence of protective efficacy 9 years after vaccination (48,51). The duration of protective efficacy for adolescents who were vaccinated during infancy or childhood must be evaluated; the results will determine future recommendations concerning booster doses.

3. Flexible dosage schedules are required to effectively integrate hepatitis B vaccine into current and future immunization programs for infants. Schedules may change as optimum dosage and timing are studied and new information becomes available.

4. Multiple-antigen vaccines that incorporate HBsAg as one component are currently being evaluated. The routine use of these vaccines may alter childhood vaccination schedules or may result in the administration of additional doses of certain antigens. However, these vaccines should greatly facilitate vaccine delivery and minimize the number of injections.

References

1. CDC. Protection against viral hepatitis: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1990;39:5-22.

2. Alter MJ, Hadler SC, Margolis HS, et al. The changing epidemiology of hepatitis B in the United States: need for alternative vaccination strategies. JAMA 1990;263:1218-22.

3. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. Semin Liver Dis 1991;11:84-92.

4. Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B virus trans- mission in the United States: prevention by passive-active immuni- zation. JAMA 1985;253:1740-5.

5. Stevens CE, Taylor PE, Tong MJ, et al. Yeast-recombinant hepatitis B vaccine: efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. JAMA 1987;257:2612-6.

6. McMahon BJ, Rhoades ER, Heyward WL, et al. A comprehensive programme to reduce the incidence of hepatitis B virus infection and its sequelae in Alaskan Natives. Lancet 1987;2:1134-6.

7. Stevens CE, Neurath RA, Beasley RP, Szmuness W. HBeAg and anti-HBe detection by radioimmunoassay: correlation with vertical transmission of hepatitis B virus in Taiwan. J Med Virol 1979;3:237-41.

8. Xu Z-Y, Liu C-B, Francis DP, et al. Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. Pediatrics 1985;76:713-8.

9. Beasley RP, Hwang L-Y. Epidemiology of hepatocellular carcinoma. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral hepatitis and liver disease. New York: Grune & Stratton, 1984:209-24.

10. Beasley RP, Hwang L-Y. Postnatal infectivity of hepatitis B surface antigen-carrier mothers. J Infect Dis 1983;147:185-90.

11. Jonas MM, Schiff ER, O'Sullivan MJ, et al. Failure of the Centers for Disease Control criteria to identify hepatitis B infection in a large municipal obstetrical population. Ann Intern Med 1987;107:335-7.

12. Kumar ML, Dawson NV, McCullough AJ, et al. Should all pregnant women be screened for hepatitis B? Ann Intern Med 1987;107:273-7.

13. American Academy of Pediatrics. Hepatitis B. In: Peter G, Lepow ML, McCracken GH, Phillips CF, eds. Report of the Committee on Infectious Diseases. 22nd ed. Elk Grove Village, IL: American Academy of Pedia- trics, 1991:238-55.

14. American Academy of Pediatrics and American College of Obsterics and Gynecology. Guidelines for prenatal care. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics, 1991 (in press).

15. McMahon BJ, Alward WLM, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985;151: 599-603.

16. World Health Organization. Progress in the control of viral hepatitis: memorandum from a WHO meeting. Bull WHO 1988;66:443-55.

17. Schreeder MT, Bender TR, McMahon BJ, et al. Prevalence of hepatitis B in selected Alaskan Eskimo villages. Am J Epidemiol 1983;118:543-9.

18. Wong DC, Purcell RH, Rosen L. Prevalence of antibody to hepatitis A and hepatitis B viruses in selected populations of the South Pacific. Am J Epidemiol 1979;110:227-36.

19. Franks AL, Berg CJ, Kane MA, et al. Hepatitis B virus infection among children born in the United States to Southeast Asian refugees. N Engl J Med 1989;321:1301-5.

20. Hurie MB, Mast EE, Davis JP. Horizontal transmission of hepatitis B virus infection to United States-born children of Hmong refugees. Pediatrics 1992 (in press).

21. McQuillan GM, Townsend TR, Fields HA, et al. The seroepidemiology of hepatitis B virus in the United States, 1976 to 1980. Am J Med 1989;87 (Suppl 3A):5-10.

22. CDC. Racial differences in rates of hepatitis B virus infection -- United States, 1976-1980. MMWR 1989;38:818-21.

23. Moyer LA, Shapiro CN, Shulman G, Brugliera P. A survey of hepatitis B surface antigen positive blood donors: degree of understanding and action taken after notification. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:728-9.

24. US Department of Labor, US Department of Health and Human Services. Joint Advisory Notice. Protection against exposure to hepatitis B virus (HBV) and human immunodeficiency virus (HIV).

Federal Register 1987;52: 41818-24.

25. Rizzetto M. The delta agent. Hepatology 1983;3:729-37.

26. Hadler SC, Fields HA. Hepatitis delta virus. In: Belshe RB, ed. Textbook of human virology. St. Louis: Mosby Year Book, 1991:749-66.

27. Perrillo RP, Schiff ER, Davis FL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. N Engl J Med 1990;323:295-301.

28. Arevalo JA, Washington E. Cost-effectiveness of prenatal screening and immunization for hepatitis B virus. JAMA 1988;259:365-9.

29. CDC. Safety of therapeutic immune globulin preparations with respect to transmission for human T-lymphotrophic virus type III/lymphadenopathy- associated virus infection. MMWR 1986;35:231-3.

30. Wells MA, Wittek AE, Epstein JS, et al. Inactivation and partition of human T-cell lymphotrophic virus, type III, during ethanol fraction- ation of plasma. Transfusion 1986;26:210-3.

31. Zajac BA, West DJ, McAleer WJ, Scolnick EM. Overview of clinical studies with hepatitis B vaccine made by recombinant DNA. J Infect 1986;13(Suppl A):39-45.

32. Andre FE. Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. Am J Med 1989;87(Suppl 3A):14s-20s.

33. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demon- stration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med 1980;303:833-41.

34. Shaw FE Jr, Guess HA, Roets JM, et al. Effect of anatomic injection site, age, and smoking on the immune response to hepatitis B vaccination. Vaccine 1989;7:425-30.

35. Redfield RR, Innis BL, Scott RM, Cannon HG, Bancroft WH. Clinical evaluation of low-dose intradermally administered hepatitis B vaccine, a cost reduction strategy. JAMA 1985;254:3203-6.

36. Coleman PJ, Shaw FE Jr, Serovich J, Hadler SC, Margolis HS. Intradermal hepatitis B vaccination in a large hospital employee population. Vaccine 1991;9:723-7.

37. Gonzalez ML, Usandizaga M, Alomar P, et al. Intradermal and intramus- cular route for vaccination against hepatitis B. Vaccine 1990;8:402-5.

38. Lancaster D, Elam S, Kaiser AB. Immunogenicity of the intradermal route of hepatitis B vaccination with use of recombinant hepatitis B vaccine. Am J Infect Control 1989;17:126-9.

39. King JW, Taylor EM, Crow SD, et al. Comparison of the immunogenicity of hepatitis B vaccine administered intradermally and intramuscularly. Rev Infect Dis 1990;12:1035-43.

40. Xu Z-Y, Margolis HS. Determinants of hepatitis B vaccine efficacy and implications for vaccination strategies. Monogr Virol 1991 (in press).

41. Poovorawan Y, Sanpavat S, Pongpuniert W, Chumdermpadetsuk S, Sentrakul P, Safary A. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. JAMA 1989;261: 3278-81.

42. Jilg W, Schmidt M, Dienhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. J Infect Dis 1989;160:766-9.

43. Hadler SC, Monzon MA, Lugo DR, Perez M. Effect of timing of hepatitis B vaccine dose on response to vaccine in Yucpa Indians. Vaccine 1989;7: 106-10.

44. Coursaget P, Yvonnet B, Relyveld EH, Barres JL, Diop-Mar I, Chiron JP. Simultaneous administration of diphtheria-tetanus-pertussis-polio and hepatitis B vaccines in a simplified immunization program: Immune response to diphtheria toxoid, tetanus toxoid, pertussis and hepatitis B surface antigen. Infect Immun 1986;151:784-7.

45. Stevens CE, Alter HJ, Taylor PE, et al. Hepatitis B vaccine in patients receiving hemodialysis: immunogenicity and efficacy. N Engl J Med 1984; 311:496-501.

46. Jilg W, Schmidt M, Weinel B, et al. Immunogenicity of recombinant hepatitis B vaccine in dialysis patients. J Hepatol 1986;3:190-5.

47. Collier AC, Corey L, Murphy VL, Handsfield HH. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. Ann Intern Med 1988;109:101-5.

48. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 1986; 315:209-14.

49. Lee S-D, Lo K-J, Wu J-C, et al. Prevention of maternal-infant hepatitis B virus transmission by immunization: role of serum hepatitis B virus DNA. Hepatology 1986;6:369-73.

50. Francis DP, Hadler SC, Thompson SE, et al. Prevention of hepatitis B with vaccine: report from the Centers for Disease Control multi-center efficacy trial among homosexual men. Ann Intern Med 1982;97:362-6.

51. Wainwright RB, McMahon BJ, Bulkow LR, et al. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. JAMA 1989;261:2362-6.

52. Lo K-J, Lee S-D, Tsai Y-T, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in infants born to HBeAg-positive HBsAg-carrier mothers. Hepatology 1988;8:1647-50.

53. Hwang L-Y, Lee C-Y, Beasley RP. Five year follow-up of HBV vaccination with plasma-derived vaccine in neonates. Evaluation of immunogenicity and efficacy against perinatal transmission. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:759-61.

54. Shaw FE Jr, Graham DJ, Guess HA, et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination: experience of the first three years. Am J Epidemiol 1988;127:337-52.

55. Chen D-S. Control of hepatitis B in Asia: mass immunization program in Taiwan. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:716-9.

56. CDC. Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues and semen for evidence of hepatitis B and hepatitis C. MMWR 1991;40:5-6.

57. Beasley RP, Hwang L-Y, Stevens CE, et al. Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B virus carrier state: final report of a randomized double-blind, placebo-controlled trial. Hepatology 1983;3:135-41.

58. CDC. Guidelines for prevention of transmission of human immunodefi- ciency virus and hepatitis B virus to health-care and public-safety workers. MMWR 1989;38(Suppl 6):5-15.

59. Department of Labor. Occupational exposure to bloodborne pathogens: proposed rule and notice of hearing. Federal Register 1989;54: 23042-139.

60. Breuer B, Friedman SM, Millner ES, Kane MA, Snyder RH, Maynard JE. Transmission of hepatitis B virus in classroom contacts of mentally retarded carriers. JAMA 1985;254:3190-5.

61. Seaworth B, Drucker J, Starling J, Drucker R, Stevens C, Hamilton J. Hepatitis B vaccines in patients with chronic renal failure before dialysis. J Infect Dis 1988;157:332-7.

62. Moyer LA, Alter MJ, Favero MS. Hemodialysis-associated hepatitis B: revised recommendations for serologic screening. Semin Dialysis 1990;3: 201-4.

63. Hershow RC, Hadler SC, Kane MA. Adoption of children from countries with endemic hepatitis B: transmission risks and medical issues. Pediatr Infect Dis J 1987;6:431-7.

If a four-dose schedule is used (Table_1 and Table_3), the second and third doses should be administered at 1 and 2 months of age, respec- tively, and the fourth dose at 12-18 months of age.

Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 1. Recommended doses of currently licensed hepatitis B vaccines

Group	Recombivax HB * Dose (ug)	(mL)	Engerix-B * Dose (ug)	(mL)
Infants of HBsAg + -negative mothers and children <11 years	2.5	(0.25)	10	(0.5)
Infants of HBsAg-positive mothers; prevention of perinatal infection	5	(0.5)	10	(0.5)
Children and adolescents 11-19 years	5	(0.5)	20	(1.0)
Adults >=20 years	10	(1.0)	20	(1.0)
Dialysis patients and other immunocompromised persons	40	(1.0) &	40	(2.0) @

* Both vaccines are routinely administered in a three-dose series. Engerix-B has also been licensed for a four-dose series administered at 0, 1, 2, and 12 months.
+ HBsAg = Hepatitis B surface antigen.
& Special formulation.
@ Two 1.0-mL doses administered at one site, in a four-dose schedule at 0, 1, 2, and 6 months.

Return to top.

Table_2

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 2. Guide to postexposure immunoprophylaxis for exposure to hepatitis B virus

Type of exposure	Immunoprophylaxis	Reference
Perinatal	Vaccination + HBIG *	p. 11-12
Sexual -- acute infection	HBIG +/- Vaccination	Appendix
Sexual -- chronic carrier	Vaccination	p. 12, 15

Household contact -- chronic carrier	Vaccination	p. 12, 15
Household contact -- acute case	None unless known exposure	Appendix
Household contact -- acute case, known exposure	HBIG +/- vaccination	Appendix
Infant (<12 months) -- acute case in primary care-giver	HBIG + vaccination	Appendix
Inadvertent -- percutaneous/ permucosal	Vaccination +/- HBIG	Appendix

* HBIG = Hepatitis B immune globulin.

Return to top.

Table_3

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 3. Recommended schedule of hepatitis B immunoprophylaxis to prevent perinatal transmission of hepatitis B virus infection

Infant born to mother known to be HBsAg * positive	
Vaccine dose +	Age of infant
First	Birth (within 12 hours)
HBIG &	Birth (within 12 hours)
Second	1 month
Third	6 months @
Infant born to mother not screened for HBsAg	
Vaccine dose **	Age of infant
First	Birth (within 12 hours)
HBIG &	If mother is found to be HBsAg positive, administer dose to infant as soon as possible, not later than 1 week after birth
Second	1-2 months ++
Third	6 months @

* HBsAg = Hepatitis B surface antigen.
+ See Table 1 for appropriate vaccine dose.
& Hepatitis B immune globulin (HBIG) -- 0.5 mL administered intramuscularly at a site different from that used for vaccine.
@ If four-dose schedule (Engerix-B) is used, the third dose is administered at 2 months of age and the fourth dose at 12-18 months.
** First dose = dose for infant of HBsAg-positive mother (see Table 1). If mother is found to be HBsAg positive, continue that dose; if mother is found to be HBsAg negative, use appropriate dose from Table 1.
++ Infants of women who are HBsAg negative can be vaccinated at 2 months of age.

Return to top.

Table_4

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 4. Recommended schedules of hepatitis B vaccination for infants born to HBsAg * -negative mothers

Hepatitis B vaccine	Age of infant
Option 1	
Dose 1	Birth -- before hospital discharge
Dose 2	1-2 months +
Dose 3	6-18 months +
Option 2	
Dose 1	1-2 months +
Dose 2	4 months +
Dose 3	6-18 months +

* HBsAg = Hepatitis B surface antigen.
+ Hepatitis B vaccine can be administered simultaneously with diphtheria-tetanus-pertussis, Haemophilus influenzae type b conjugate, measles-mumps-rubella, and oral polio vaccines at the same visit.

Return to top.

Page converted: 08/05/98

SAFER·HEALTHIER·PEOPLE™
Morbidity and Mortality Weekly Report
Centers for Disease Control and Prevention
1600 Clifton Rd, MailStop E-90, Atlanta, GA 30333, U.S.A

USA.gov Government Made Easy
Department of Health and Human Services

This page last reviewed 5/2/01

MMWR
Recommendations and Reports
June 16, 1995 / 44(RR-5);1-9

Recommended Childhood Immunization Schedule -- United States, 1995

Working Group

Thomas L. Copmann, Ph.D. Michele Kiely, M.D. Pharmaceutical Research and Maternal and Child Health Bureau

Manufacturers of America Health Resources Management

Administration Jeffrey P. Davis, M.D. Advisory Committee on Immunization Georges Peter, M.D.

Practices American Academy of Pediatrics

Kathryn M. Edwards, M.D. Fred E. Thompson, M.D. Advisory Committee on Immunization Advisory Committee on Immunization

Practices Practices

Caroline B. Hall, M.D. Gina Rabinovitch, M.D. American Academy of Pediatrics National Institutes of Health

Neal A. Halsey, M.D. David R. Smith, M.D. Advisory Committee on Immunization Immunization Grantee Working Group

Practices American Academy of Pediatrics Richard K. Zimmerman, M.D.

American Academy of Family Carolyn Hardegree, M.D. Physicians Food and Drug Administration

The following CDC staff members prepared this report:

Jacqueline S. Gindler, M.D.

Stephen C. Hadler, M.D. Peter M. Strebel, M.B.Ch.B., M.P.H.

John C. Watson, M.D., M.P.H.

Epidemiology and Surveillance Division

Summary

The need for a single childhood immunization schedule prompted the unification of previous vaccine recommendations made by the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP). In addition to presenting the newly recommended schedule for the administration of vaccines during childhood, this report addresses the previous differences between the AAP and ACIP childhood vaccination schedules and the rationale for changing previous recommendations.

INTRODUCTION

Since 1988, the U.S. childhood immunization schedule has rapidly expanded to accommodate the introduction of new, universally recommended vaccines (i.e., Haemophilus influenzae type b {Hib} conjugate {1,2} and hepatitis B {2,3} vaccines) and recommendations for a second dose of measles-mumps-rubella vaccine (MMR) (4,5) and the use of acellular pertussis vaccines (2,6). For approximately 30 years, the Advisory Committee on Immunization Practices (ACIP) and the Committee on Infectious Diseases (COID) of the American Academy of Pediatrics (AAP) -- the two groups responsible for developing vaccine recommendations for the public and private sectors -- worked to develop similar schedules for routine childhood vaccination. However, some differences in the two schedules persisted. The unification of these childhood immunization schedules is essential to issuing consistent recommendations for both private and public health practitioners and for parents.

In February 1994, a working group was convened comprising members of AAP, ACIP, the American Academy of Family Physicians (AAFP), the Food and Drug Administration (FDA), the National Institutes of Health, and CDC. Representatives from state immunization programs, the Maternal and Child Health Bureau of the Health Resources and Services Administration, and vaccine manufacturers also participated. The objective of this working group was to develop a single, scientifically valid childhood immunization schedule -- presented in an easily comprehensible format -- that would accommodate the current recommendations of both ACIP and AAP and ensure the timely vaccination of preschool-age children. The schedule would identify a specified age for administering each vaccine dose and provide an acceptable range of ages to ensure flexibility for health-care providers. The working group also addressed the number of antigens and injections that should be administered at each visit, the number of visits required for children by 2 years of age, the availability of combined diphtheria and tetanus toxoids and pertussis (DTP)-Hib vaccines, and the capacity of the schedule to accommodate newly licensed vaccines (e.g., varicella vaccine). This report presents the recommended childhood immunization schedule (approved by ACIP, AAP, and AAFP) (Table_1) and the rationale for changing the previous recommendations. Practitioners should consult the Report of the Committee on Infectious Diseases (Red Book) (2), the vaccine-specific recommendations of ACIP, and the official manufacturers' package inserts or the Physician's Desk Reference (PDR) (7) for detailed information and specific recommendations for administration of vaccines.

RATIONALE FOR CHANGE AND CURRENT RECOMMENDATIONS

In 1994, the substantial differences between the recommended AAP and ACIP schedules included the schedule for infant hepatitis B vaccination and the timing of the third dose of oral poliovirus vaccine (OPV) and the second dose of MMR (Table_2). Resolution of the differences between the schedules is described in the following sections.

OPV

Since 1963, OPV has been the recommended vaccine for inducing long-lasting immunity to poliomyelitis. The primary series has consisted of two doses administered during infancy at approximately 2-month intervals beginning at 6 8 weeks of age, a third dose recommended at 6 weeks to 14 months after the second dose (generally administered at 15-18 months of age), and a fourth dose administered at 4-6 years of age. In late 1993, ACIP recommended that the third dose of OPV be administered at 6 months of age (8), whereas AAP recommended that this dose be administered at 6-18 months of age (2). A study comparing two infant immunization schedules (one recommending vaccination at approximately 2, 4, 6, and 12 months of age and one at 2, 4, and 12 months of age) indicated high seroconversion rates (i.e., 96%-100%) and similar geometric mean antibody titers (measured after three doses) when following either schedule (9). Several other studies have evaluated the seroresponse to OPV administered at 2, 4, and 6 months; 2, 4, and 12 months; and 2, 4, and 18 months of age (10-13). These data indicated excellent response to all serotypes of OPV when the third dose was administered at 6, 12, or 18 months of age (Table_3).

Recommendation: Because immune response is not affected by administering the third dose of OPV at as early as 6 months of age, and because earlier scheduling can ensure a higher rate of completion of the OPV primary series at a younger age, the third dose of OPV should be administered routinely at 6 months of age. Vaccination at as late as 18 months of age remains an acceptable alternative.

MMR

First Dose

During 1989 and 1990, more than 55,000 cases of measles were reported in the United States. Nearly 25% of these cases occurred among children less than or equal to 15 months of age, including approximately 9% among children 12-15 months of age (CDC, unpublished data). At that time, the recommended age for routine measles vaccination was 15 months of age. Recent studies have examined the impact of vaccine-induced immunity on maternally derived transplacental antibody levels; these studies have indicated that younger women (i.e., women who were born after 1956 and who are therefore more likely to have vaccine-induced immunity) transfer lower titers of measles antibodies to their newborn infants than older women (who are more likely to have had natural measles infection). The transplacental antibody acquired by these younger mothers' infants wanes earlier, causing their children to become susceptible to measles at a younger age (14,15). This finding suggests that children born to younger mothers might respond well to measles vaccine administered at 12 months of age. In one recent study in which children randomly received measles vaccine at either 12 or 15 months of age (16), the measles antibody response to MMR was 93% when the vaccine was administered at 12 months of age; at 15 months of age, the antibody response was 98%. Among children of mothers born after 1961, who probably had received measles vaccine and were less likely to have had measles infection than women born in previous years, the seroconversion rate was 96% among children vaccinated at 12 months of age and 98% among those vaccinated at 15 months of age.

Recommendation: The slightly lower response to the first dose of measles vaccine when administered at 12 months of age compared with administration at 15 months of age has limited clinical importance because a second dose of MMR is recommended routinely for all children, enhancing the likelihood of seroconversion among children who do not respond to the first dose. In addition, earlier scheduling of the first dose of measles vaccine can improve vaccination coverage. In 1994, both AAP and ACIP recommended administration of the first dose of MMR vaccine at 12-15 months of age (2,8); this schedule is still recommended.

Second Dose

In 1989, both ACIP and AAP recommended that all children receive a second dose of measles-containing vaccine; however, ACIP recommended administering the second dose at 4-6 years of age (5), and AAP recommended this dose at 11-12 years of age (4). Most states have implemented school entry requirements based on one or both of these recommendations. Currently, 12 states require administration

of the second dose of measles vaccine before children enter kindergarten (i.e., at 4-6 years of age), 12 require this dose before entry to middle school (i.e., at 11-12 years of age), and 13 states require that the second dose be administered before children enter either kindergarten or middle school.

Recommendation: Because response to the second dose is high when administered to children in either age group (CDC, unpublished data), and because state-specific laws govern the administration of the second dose of MMR, the second dose of MMR can be administered at either 4-6 years of age or 11-12 years of age.

Hepatitis B

Universal hepatitis B vaccination of infants was recommended in 1991 (3,17). Although a protective serologic response (i.e., greater than or equal to 10 mIU/mL) has been demonstrated in >95% of hepatitis B vaccine recipients who received vaccine according to several schedules beginning at birth or 2 months of age (Table_4), higher antibody titers were achieved when the third dose was administered at 12 or 15 months of age (18,19). Available data indicate that higher titers of antibody ensure longer persistence of antibody (20-22); however, the effect of high antibody levels on long-term protection against disease is not known.

Recommendation: The routine hepatitis B vaccination series should begin at birth, with the second dose administered at 2 months of age, for infants whose mothers are hepatitis B surface antigen (HBsAg) negative. Acceptable ranges are from birth through 2 months of age for the first dose and from 1 through 4 months of age for the second dose, provided that at least 1 month elapses between these doses. The third dose should be administered at 6-18 months of age. Limited available data suggest an augmented response when the third dose is administered after 12 months of age (Merck Research Laboratories, unpublished data, 1994). Infants of HBsAg-positive mothers should receive the first dose of vaccine at birth (along with immunoprophylaxis with hepatitis B immune globulin); the second dose at 1 month of age; and the third dose at 6 months of age.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine (DTP)

Since the late 1940s, the approved schedule for DTP has consisted of a primary series of three doses administered at 4-8 week intervals and a fourth (i.e., reinforcing) dose administered 6-12 months after the third dose. Although the fourth dose has been administered routinely at 15-18 months of age, it may be administered as early as 12 months of age, provided that at least 6 months elapse between the third and fourth dose. No recent data are available comparing the immunogenicity of DTP or diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) when administered at 12-14 months with immunogenicity at 15-18 months of age when vaccine is either administered alone or simultaneously with MMR and Hib vaccines.

Recommendation: The current schedule for DTP vaccination is still recommended -- including the option that the fourth dose may be administered at as early as 12 months of age if 6 months elapse after the third dose. Thus, the fourth dose of DTP can be scheduled with other vaccines that are administered at 12-18 months of age. DTaP currently is licensed for use only as the fourth and/or fifth dose of the DTP series for children greater than or equal to 15 months of age (2,6).

Tetanus and Diphtheria Toxoids, Adsorbed, For Adult Use (Td)

For most persons who received a dose of DTP vaccine at 4-6 years of age, the first dose of Td is administered at 14-16 years of age and every 10 years thereafter to maintain adequate protection against tetanus and diphtheria (6). A recent U.S. serologic survey of tetanus immunity (23) indicated that tetanus immunity in the majority of the population decreases with time after the administration of the recipient's most recent vaccination. Among persons 6-16 years of age who had received their most recent tetanus vaccination 6-10 years previously, 28% had tetanus antibody titers lower than protective levels, which suggested that Td could be administered as early as 11-12 years of age.

Recommendation: The booster dose of Td should be administered at 11- 12 years of age, although vaccination at 14-16 years of age is an acceptable alternative. The earlier scheduling of this dose at 11-12 years of age encourages a routine preadolescent preventive care visit. During this visit, the practitioner should also administer a second dose of measles-containing vaccine to those persons who have not already received this dose and should ensure that children who previously have not received hepatitis B vaccine begin the vaccination series. Adolescent hepatitis B vaccination currently is recommended by AAP (2); ACIP will issue a similar recommendation. A routine visit at 11-12 years of age also will facilitate administration of other needed vaccines to adolescents.

SIMULTANEOUS ADMINISTRATION OF MULTIPLE VACCINES

Simultaneous administration of vaccines has been recommended through the administration of combined vaccines (e.g., DTP vaccine, trivalent OPV, and MMR vaccine) or administration of multiple vaccines at different sites or by different routes (e.g., simultaneous administration of DTP, OPV, and Hib). Several studies have examined the safety and immunogenicity of simultaneously administered MMR and Hib (24,25); DTP, OPV, and MMR (26,27); DTP, OPV, and Hib (25,28); hepatitis B, DTP, and OPV (29-31); and hepatitis B and MMR (Merck Research Laboratories, unpublished data, 1993). Hepatitis B vaccine, the vaccine most recently licensed for use among infants, has been shown to be safe and effective when administered from birth through 15 months of age with other routinely recommended childhood vaccines (D. Greenberg, personal communication, 1994) (32). The available safety and immunogenicity data for vaccines currently recommended by ACIP and AAP have been reviewed recently (33). Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTP, OPV, MMR, and Hib vaccines, with or without hepatitis B vaccine), data from numerous studies have indicated no interference between routinely recommended childhood vaccines (either live, atttenuated or killed) (33). These findings support the simultaneous use of all vaccines as recommended.

CONCLUSION

The development of a unified childhood immunization schedule approved by ACIP, AAP, and AAFP represents the beginning of a process that will ensure continued collaboration among the recommending groups, the pharmaceutical manufacturing industry, and FDA to maintain and work toward further simplification of a unified schedule. The recommended childhood immunization schedule will be updated and published annually.

Since the development of these recommendations in January 1995, FDA has licensed varicella zoster virus vaccine for use among susceptible persons greater than or equal to 12 months of age. The ACIP will publish recommendations for this new vaccine, and these recommendations will be incorporated into the 1996 Recommended Childhood Immunization Schedule.

References

1. ACIP. Haemophilus b conjugate vaccines for prevention of Haemophilus influenzae type b disease among infants and children two months of age and older: recommendations of the Immunization Practices Advisory Committee. MMWR 1991;40(No. RR-1):1-7.

2. American Academy of Pediatrics. Active and passive immunization. In: Peter G, ed. 1994 Red Book: report of the Committee on Infectious Diseases. 23rd ed. Elk Grove Village, IL: American Academy of Pediatrics, 1994:1-67.

3. ACIP. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee. MMWR 1991;40(No. RR-13):1-25.

4. American Academy of Pediatrics, Committee on Infectious Diseases. Measles: reassessment of the current immunization policy. Pediatrics 1989;84:110-1.

5. ACIP. Measles prevention: recommendations of the Immunization Practices Advisory Com-mittee (ACIP). MMWR 1989;38(No. S-9):1-18.

6. ACIP. Pertussis vaccination: acellular pertussis vaccine for reinforcing and booster use -- supplementary ACIP statement: recommendations of the Advisory Committee on Immunization Practices. MMWR 1992;41(No. RR-1):1-10.

7. Medical Economics Company. Physician's desk reference. 49th ed. Montvale, NJ: Medical Economics Company Inc, 1995.

8. ACIP. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1994;43(No. RR-1):1-38.

9. Hardy GE, Hopkins CC, Linnemann CC, Hatch MH, Chambers JC, Witte JJ. Trivalent oral poliovirus vaccine: a comparison of two infant immunization schedules. Pediatrics 1970;45:444-8.

10. Cohen-Abbo A, Culley BS, Reed GW, et al. Seroresponse to trivalent oral poliovirus vaccine as a function of dosage interval. Pediatr Infect Dis J 1995;4:100-6.

11. Faden H, Modlin JF, Thomas ML, McBean AM, Ferdon MB, Ogra PL. Comparative evaluation of immunization with live attenuated and enhanced-potency inactivated trivalent poliovirus vaccines in childhood: systemic and local immune responses. J Infect Dis 1990;162:1291-7.

12. McBean AM, Thoms ML, Albrecht P, Cuthie JC, Bernier R. Serologic response to oral polio vaccine and enhanced-potency inactivated polio vaccines. Am J Epidemiol 1988;128:615-28.

13. Modlin JF, Halsey NA, Thoms ML, Meschievitz CK, Patriarca P. Serum neutralizing antibody response to three experimental sequential IPV-OPV immunization schedules {Abstract}. In: Programs and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. New Orleans, LA: ICAAC, 1993.

14. Lennon JL, Black FL. Maternally derived measles immunity in era of vaccine-protected mothers. J Pediatr 1986;108:671-6.

15. Jenks PJ, Caul EO, Roome AP. Maternally derived measles immunity in children of naturally infected and vaccinated mothers. Epidemiol Infect 1988;101:473-6.

16. King GE, Markowitz LE. A comparison of seroconversion rates to MMR vaccine of children vaccinated at 9, 12, or 15 months of age {Abstract}. In: Programs and abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, FL: ICAAC, 1994.

17. American Academy of Pediatrics, Committee on Infectious Diseases. Universal hepatitis B immunization. Pediatrics 1992;89:795-800.

18. Keyserling HL, West DJ, Hesley TM, Bosley C, Wiens BL, Calandra GB. Antibody responses of healthy infants to a recombinant hepatitis B vaccine administered at two, four, and twelve or fifteen months of age. J Pediatr 1994;125:67-9.

19. Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. J Infect Dis 1989;160:766-9.

20. Stevens CE, Toy PT, Taylor PE, Lee T, Yip H. Prospects for control of hepatitis B virus infection: implications of childhood vaccination and long-term protection. Pediatrics 1992;20(suppl): 170-3.

21. Wainwright RB, McMahon BJ, Bulkow LR, et al. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. JAMA 1989;261:2362-6.

22. Jilg W, Schmidt M, Deinhardt F. Persistence of specific antibodies after hepatitis B vaccination. J Hepatol 1988;6:201-7.

23. Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G. A population-based serological survey of tetanus immunity: implications for U.S. vaccination policy. N Engl J Med 1995 (in press).

24. Steinhoff MC, Thomas ML, Dannelfelser S, O'Donovan C. Immunogenicity of H. influenzae type B-CRM197 conjugate vaccine (HbOC) given simultaneously with routine childhood immunizations. Pediatr Res 1990;27:184A.

25. Dashefsky B, Wald E, Guerra N, Byers C. Safety, tolerability, and immunogenicity of concurrent administration of Haemophilus influenzae type b conjugate vaccine (meningococcal protein conjugate) with either measles-mumps-rubella vaccine or diphtheria-tetanus-pertussis and oral poliovirus vaccines in 14- to 23-month old infants. Pediatrics 1990;85(suppl):682-9.

26. Deforest A, Long SS, Lischner HW, et al. Simultaneous administration of measles-mumps-rubella vaccine with booster doses of diphtheria-tetanus-pertussis and poliovirus vaccines. Pediatrics 1988;81:237-46.

27. Berger R, Just M. Lack of interference between vaccines {Letter}. Pediatr Infect Dis J 1983;2:172.

28. Booy R, Moxon ER, MacFarlane JA, Mayon-White RT, Slack MPE. Efficacy of Haemophilus influenzae type B conjugate vaccine in Oxford Region {Letter}. Lancet 1992;340:847.

29. Greenberg DP, Vadheim SM, Marcy SM, Wong V, Margolis H, Ward JI. Safety and immunogenicity of two recombinant hepatitis B vaccines given to 5000 infants as part of routine immunization at 2, 4, and 6 months of age. In: Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL: ICAAC, 1991.

30. Huang LM, Lee CY, Hsu CY, et al. Effect of monovalent measles and trivalent measles-mumps-rubella vaccines at various ages and concurrent administration with hepatitis B vaccine. Pediatr Infect Dis J 1990;9:461-5.

31. Barone P, Mauro L, Leonardi S, et al. Simultaneous administration of HB recombinant vaccine with diphtheria and tetanus toxoid and oral polio vaccine: a pilot study. Acta Paediatr Jpn 1991;33:455-8.

32. Greenberg DP, Vadheim CM, Marcy SM, et al. Comparative safety and immunogenicity of two recombinant Hepatitis B (HBV) vaccines given to infants at 2, 4, and 6 months of age {Abstract}. In: Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Anaheim, CA: ICAAC, 1992:264.

33. King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. Pediatr Infect Dis J 1994;13:394-407.

Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 1. Recommended childhood immunization schedule *+ -- United States, January 1995

Vaccine	Birth	2 Months	4 Months	6 Months	12 & Months	15 Months	18 Months	4 - 6 Years	11-12 Years	14-16 Years
Hepatitis B @	º- HB-1 ----------º		º- HB-2 ----------º		º- HB-3 ----------º					
Diphtheria-Tetanus-Pertussis (DTP) **		DTP	DTP	DTP	º- DTP or º- or DTaP >= at 15 months ---º			DTP or DTaP	º- Td----------º	

```
Haemophilus                          Hib       Hib        Hib   º- Hib -------------º
  influenzae type b ++

Poliovirus                           OPV       OPV    º- OPV ---------------------------------º     OPV

Measles-Mumps-                                                  º- MMR -------------º              MMR   or  MMR
  Rubella &&
-------------------------------------------------------------------------------------------------------------------------------
 * Recommended vaccines are listed under the routinely recommended ages. Shaded bars
   indicate range of acceptable ages for vaccination.
 + Although no changes have been made to this schedule since publication in MMWR (weekly)
   in January 1995, this table has been revised to more accurately reflect the recommendations.
 & Vaccines recommended for administration at 12-15 months of age may be administered at
   either one or two visits.
 @ Infants born to hepatitis B surface antigen (HBsAg)-negative mothers should receive the
   second dose of hepatitis B vaccine between 1 and 4 months of age, provided at least
   1 month has elapsed since receipt of the first dose. The third dose is recommended between
   6 and 18 months of age. Infants born to HBsAg-positive mothers should receive
   immunoprophylaxis for hepatitis B with 0.5 mL Hepatitis B Immune Globulin (HBIG) within
   12 hours of birth, and 5 ug of either Merck, Sharpe, & Dohme (West Point, Pennsylvania)
   vaccine (Recombivax HB (R)) or 10 ug of SmithKline Beecham (Philadelphia) vaccine
   (Engerix-B (R)) at a separate site. For these infants, the second dose of vaccine is
   recommended at 1 month of age and the third dose at 6 months of age. All pregnant women
   should be screened for HBsAg during an early prenatal visit.
** The fourth dose of DTP may be administered as early as 12 months of age, provided at
   least 6 months have elapsed since the third dose of DTP. Combined DTP-Hib products may
   be used when these two vaccines are administered simultaneously. Diphtheria and tetanus
   toxoids and acellular pertussis vaccine (DTaP) is licensed for use for the fourth and/or fifth
   dose of DTP in children >=15 months of age and may be preferred for these doses in children
   in this age group.
++ Three H. influenzae type b conjugate vaccines are available for use in infants:
   a) oligosaccharide conjugate Hib vaccine (HbOC) (HibTITER (R), manufactured by Praxis
   Biologics, Inc. {West Henrietta, New York} and distributed by Lederle-Praxis Biologicals
   {Wayne, New Jersey}); b) polyribosylribitol phosphate-tetanus toxoid conjugate (PRP-T)
   (ActHIB (TM), manufactured by Pasteur Merieux Serums & Vaccins, S.A. {Lyon, France} and
   distributed by Connaught Laboratories, Inc. {Swiftwater, Pennsylvania}, and OmniHIB (TM),
   manufactured by Pasteur Merieux Serums & Vaccins, S.A. and distributed by SmithKline
   Beecham); and c) Haemophilus b conjugate vaccine (Meningococcal Protein Conjugate)
   (PRP-OMP) (PedvaxHIB (R), manufactured by Merck, Sharp, & Dohme). Children who have
   received PRP-OMP at 2 and 4 months of age do not require a dose at 6 months of age.
   After the primary infant Hib conjugate vaccine series is completed, any licensed Hib
   conjugate vaccine may be administered as a booster dose at age 12-15 months.
&& The second dose of MMR vaccine should be administered EITHER at 4-6 years of age OR
   at 11-12 years of age.

Source: Advisory Committee on Immunization Practices, American Academy of Pediatrics, and
American Academy of Family Physicians.
===============================================================================================================================
```

Return to top.

Table_2

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 2. Differences between the American Academy of Pediatrics' (AAP) and the Advisory Committee on Immunization Practices' (ACIP) childhood immunization schedules, by selected vaccine -- United States, 1994

Vaccine or vaccine dose	AAP recommendation	ACIP recommendation
OPV-3 *	6-18 mos	6 mos
Hepatitis B	0-2, 1-4, + 6-18 mos	Birth, 1-2, 6-18 mos OR 2, 4, 6-18 mos
MMR-2 &	11-12 yrs	4-6 yrs

* The third dose of oral poliovirus vaccine.
+ Provided that at least 1 month has elapsed between the first and second doses.
& The second dose of measles-mumps-rubella vaccine.

Return to top.

Table_3

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 3. Percentage of children with serum-neutralizing antibody to poliovirus types 1 (p1), 2 (p2), and 3 (p3) after two and three doses of oral poliovirus vaccine, by age at vaccination and study

Age at vaccination	After two doses (%)	After three doses (%)

(mos)	Study	p1	p2	p3	p1	p2	p3
2, 4, 6	Hardy (9)	93	100	91	97	100	96
	Cohen-Abbo (10)	89	100	93	99	100	99
2, 4, 12	Hardy (9)	92	99	90	96	100	96
	Faden (11)	100	100	100	100	100	100
2, 4, 18	McBean (12)	92	100	96	97	100	100
	Modlin (13)	95	100	90	95	100	100

Return to top.

Table_4

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 4. Percentage of children who seroconverted and geometric mean titers (GMTs) after vaccination with hepatitis B vaccine, by ageat first dose and vaccination schedule

Age at first dose/ Vaccination schedule (mos)	Total no. children	No. mos between first dose and measurement	No. doses received *	Percentage of children who seroconverted +	GMT
Birth					
0, 1, 2, 12	62	9	3	95	110
	46	13	4	100	647
0, 1, 6	78	9	3	96	262
0, 2, 4	49	9	3	98	99
0, 2, 6	50	9	3	98	216
2 mos					
2, 4, 6	82	7	3	98	202
2, 4, 6, 15 &	32	14	4	100	1,793
2, 4, 12	41	11	3	100	1,633
2, 4, 12 (18)	52	11	3	98	1,358
2, 4, 15	38	14	3	97	1,527
2, 4, 15 (18)	50	14	3	100	3,424

* At the time of measurement.
\+ Children who had >=10 mIU/mL of antibody to hepatitis B surface antigen.
& A subset of the infants vaccinated at 2, 4, and 6 months of age.

Source: David West, Merck Research Laboratories.

Return to top.

Page converted: 09/19/98

SAFER·HEALTHIER·PEOPLE™
Morbidity and Mortality Weekly Report
Centers for Disease Control and Prevention
1600 Clifton Rd, MailStop E-90, Atlanta, GA 30333, U.S.A

USA.gov Government Made Easy
Department of Health and Human Services

This page last reviewed 5/2/01

Footnote 5

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Enbrel safely and effectively. See full prescribing information for Enbrel.

Enbrel® (etanercept)
Solution for Subcutaneous Use
Initial U.S. Approval: 1998

WARNINGS:
SERIOUS INFECTIONS AND MALIGNANCIES
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. (5.1)**
- **Enbrel should be discontinued if a patient develops a serious infection or sepsis during treatment. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting Enbrel. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

MALIGNANCIES

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel. (5.3)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	09/2011
Dosage and Administration, Monitoring to Assess Safety (2.5)	09/2011
Warnings and Precautions, Serious Infections (5.1)	09/2011
Warnings and Precautions, Malignancies (5.3)	02/2011

----------INDICATIONS AND USAGE----------

Enbrel is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA) (1.1)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older (1.2)
- Psoriatic Arthritis (PsA) (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Plaque Psoriasis (PsO) (1.5)

----------DOSAGE AND ADMINISTRATION----------

Enbrel is administered by subcutaneous injection.

- Adult RA and PsA (2.1)
  50 mg once weekly with or without methotrexate (MTX)
- AS (2.1)
  50 mg once weekly
- Adult PsO (2.2)
  50 mg twice weekly for 3 months, followed by 50 mg once weekly
- JIA (2.3)
  0.8 mg/kg weekly, with a maximum of 50 mg per week

----------DOSAGE FORMS AND STRENGTHS----------

- 50 mg Single-use Prefilled Syringe (3)
  0.98 mL of a 50 mg/mL solution of etanercept
- 50 mg Single-use Prefilled SureClick® Autoinjector (3)
  0.98 mL of a 50 mg/mL solution of etanercept
- 25 mg Single-use Prefilled Syringe (3)
  0.51 mL of a 50 mg/mL solution of etanercept
- 25 mg Multiple-use Vial (3)
  25 mg of etanercept

----------CONTRAINDICATIONS----------

- Sepsis (4)

----------WARNINGS AND PRECAUTIONS----------

- Do not start Enbrel during an active infection. If an infection develops, monitor carefully and stop Enbrel if infection becomes serious. (5.1)
- Consider empiric anti-fungal therapy for patients at risk for invasive fungal infections who develop a severe systemic illness on Enbrel (those who reside or travel to regions where mycoses are endemic). (5.1)
- Demyelinating disease, exacerbation or new onset, may occur. (5.2)
- Cases of lymphoma have been observed in patients receiving TNF-blocking agents. (5.3)
- Congestive heart failure, worsening or new onset, may occur. (5.4)
- Advise patients to seek immediate medical attention if symptoms of pancytopenia or aplastic anemia develop, and consider stopping Enbrel. (5.5)
- Monitor hepatitis B virus carriers for reactivation during and several months after therapy. If reactivation occurs, consider stopping Enbrel and beginning anti-viral therapy. (5.6)
- Anaphylaxis or serious allergic reactions may occur. (5.7)
- Stop Enbrel if lupus-like syndrome or autoimmune hepatitis develops. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence > 5%): infections and injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Live vaccines – should not be given with Enbrel (5.8, 7.1)
- Anakinra – increased risk of serious infection (5.12, 7.2)
- Abatacept – increased risk of serious adverse events, including infections (5.12, 7.2)
- Cyclophosphamide – use with Enbrel is not recommended (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy registry available (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS:
SERIOUS INFECTIONS AND MALIGNANCIES

SERIOUS INFECTIONS
Patients treated with Enbrel are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Enbrel should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Enbrel use and during therapy. Treatment for latent infection should be initiated prior to Enbrel use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with Enbrel should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Enbrel, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCIES
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

Enbrel is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). Enbrel can be initiated in combination with methotrexate (MTX) or used alone.

1.2 Polyarticular Juvenile Idiopathic Arthritis

Enbrel is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older.

1.3 Psoriatic Arthritis

Enbrel is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). Enbrel can be used in combination with methotrexate (MTX) in patients who do not respond adequately to MTX alone.

1.4 Ankylosing Spondylitis

Enbrel is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (AS).

1.5 Plaque Psoriasis

Enbrel is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

2 DOSAGE AND ADMINISTRATION

Table 1. Dosing and Administration for Adult Patients

Patient Population	Recommended Dosage Strength and Frequency
Adult RA, AS, and PsA Patients	50 mg weekly
Adult PsO Patients	Starting Dose: 50 mg twice weekly for 3 months Maintenance Dose: 50 mg once weekly

See the Enbrel (etanercept) "Instructions for Use" insert for detailed information on injection site selection and dose administration.

2.1 Adult Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Patients

MTX, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Enbrel.

Based on a study of 50 mg Enbrel twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar American College of Rheumatology (ACR) response rates, doses higher than 50 mg per week are not recommended.

2.2 Adult Plaque Psoriasis Patients

In addition to the 50 mg twice weekly recommended starting dose, starting doses of 25 mg or 50 mg per week were shown to be efficacious. The proportion of responders was related to Enbrel dosage *[see Clinical Studies (14.5)]*.

2.3 JIA Patients

Table 2. Dosing and Administration for Juvenile Idiopathic Arthritis

Pediatric Patients Weight	Recommended Dose
63 kg (138 pounds) or more	50 mg weekly
Less than 63 kg (138 pounds)	0.8 mg/kg weekly

In JIA patients, glucocorticoids, NSAIDs, or analgesics may be continued during treatment with Enbrel. Higher doses of Enbrel have not been studied in pediatric patients.

2.4 Preparation of Enbrel

Enbrel is intended for use under the guidance and supervision of a physician. Patients may self-inject when deemed appropriate and if they receive medical follow-up, as necessary. Patients should not self-administer until they receive proper training in how to prepare and administer the correct dose.

The Enbrel (etanercept) "Instructions for Use" insert for each presentation contains more detailed instructions on the preparation of Enbrel.

Preparation of Enbrel Using the Single-use Prefilled Syringe or Single-use Prefilled SureClick Autoinjector
Before injection, Enbrel may be allowed to reach room temperature (approximately 15 to 30 minutes). DO NOT remove the needle cover while allowing the prefilled syringe to reach room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present.

When using the Enbrel single-use prefilled syringe, check to see if the amount of liquid in the prefilled syringe falls between the two purple fill level indicator lines on the syringe. If the syringe does not have the right amount of liquid, DO NOT USE THAT SYRINGE.

Preparation of Enbrel Using the Multiple-use Vial
Enbrel should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol), giving a solution of 1.0 mL containing 25 mg of Enbrel.

A vial adapter is supplied for use when reconstituting the lyophilized powder. However, the vial adapter should not be used if multiple doses are going to be withdrawn from the vial. If the vial will be used for multiple doses, a 25-gauge needle should be used for reconstituting and withdrawing Enbrel, and the supplied "Mixing Date:" sticker should be attached to the vial and the date of reconstitution entered. Reconstituted solution must be used within 14 days. Discard reconstituted solution after 14 days because product stability and sterility cannot be assured after 14 days.

If using the vial adapter, twist the vial adapter onto the diluent syringe. Then, place the vial adapter over the Enbrel vial and insert the vial adapter into the vial stopper. Push down on the plunger to inject the diluent into the Enbrel vial. If using a 25-gauge needle to reconstitute and withdraw Enbrel, the diluent should be injected very slowly into the Enbrel vial. It is normal for some foaming to occur. Keeping the diluent syringe in place, gently swirl the contents of the Enbrel vial during dissolution. To avoid excessive foaming, do not shake or vigorously agitate.

Generally, dissolution of Enbrel takes less than 10 minutes. Do not use the solution if discolored or cloudy, or if particulate matter remains.

Withdraw the correct dose of reconstituted solution into the syringe. Some foam or bubbles may remain in the vial. Remove the syringe from the vial adapter or remove the 25-gauge needle from the syringe. Attach a 27-gauge needle to inject Enbrel.

The contents of one vial of Enbrel solution should not be mixed with, or transferred into, the contents of another vial of Enbrel. No other medications should be added to solutions containing Enbrel, and do not reconstitute Enbrel with other diluents. Do not filter reconstituted solution during preparation or administration.

2.5 Monitoring to Assess Safety

Prior to initiating Enbrel and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

50 mg Single-use Prefilled Syringe
0.98 mL of a 50 mg/mL solution of etanercept
50 mg Single-use Prefilled SureClick Autoinjector
0.98 mL of a 50 mg/mL solution of etanercept
25 mg Single-use Prefilled Syringe
0.51 mL of a 50 mg/mL solution of etanercept
25 mg Multiple-use Vial
25 mg of etanercept

4 CONTRAINDICATIONS

Enbrel should not be administered to patients with sepsis.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with Enbrel are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with Enbrel should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- With chronic or recurrent infection;
- Who have been exposed to tuberculosis;
- With a history of an opportunistic infection;
- Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- With underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes *[see Adverse Reactions (6.1)]*.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Enbrel.

Enbrel should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with Enbrel should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Tuberculosis
Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving Enbrel, including patients who have previously received treatment for latent or active tuberculosis. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with Enbrel than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been

reported for TNF blockers, including Enbrel. Tuberculosis has developed in patients who tested negative for latent tuberculosis prior to initiation of therapy. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating Enbrel and periodically during therapy. Tests for latent tuberculosis infection may be falsely negative while on therapy with Enbrel.

Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating Enbrel, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of Enbrel in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during Enbrel treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Invasive Fungal Infections

Cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including Enbrel. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric anti-fungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric anti-fungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of anti-fungal therapy. In 38 Enbrel clinical trials and 4 cohort studies in all approved indications representing 27,169 patient-years of exposure (17,696 patients) from the United States and Canada, no histoplasmosis infections were reported among patients treated with Enbrel.

5.2 Neurologic Events

Treatment with TNF-blocking agents, including Enbrel, has been associated with rare (< 0.1%) cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability, and with peripheral nervous system demyelinating disorders. Cases of transverse myelitis, optic neuritis, multiple sclerosis, Guillain-Barré syndromes, other peripheral demyelinating neuropathies, and new onset or exacerbation of seizure disorders have been reported in postmarketing experience with Enbrel therapy. Prescribers should exercise caution in considering the use of Enbrel in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders *[see Adverse Reactions (6.2)]*.

5.3 Malignancies

Lymphomas

In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared to control patients. During the controlled portions of Enbrel trials in adult patients with RA, AS, and PsA, 2 lymphomas were observed among 3306 Enbrel-treated patients versus 0 among 1521 control patients (duration of controlled treatment ranged from 3 to 36 months).

Among 6543 adult rheumatology (RA, PsA, AS) patients treated with Enbrel in controlled and uncontrolled portions of clinical trials, representing approximately 12,845 patient-years of therapy, the observed rate of lymphoma was 0.10 cases per 100 patient-years. This was 3-fold higher than the rate of lymphoma expected in the general U.S. population based on the Surveillance, Epidemiology, and End Results (SEER) Database. An increased rate of

lymphoma up to several-fold has been reported in the RA patient population, and may be further increased in patients with more severe disease activity.

Among 4410 adult PsO patients treated with Enbrel in clinical trials up to 36 months, representing approximately 4278 patient-years of therapy, the observed rate of lymphoma was 0.05 cases per 100 patient-years, which is comparable to the rate in the general population. No cases were observed in Enbrel- or placebo-treated patients during the controlled portions of these trials.

Leukemia
Cases of acute and chronic leukemia have been reported in association with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukemia.

During the controlled portions of Enbrel trials, 2 cases of leukemia were observed among 5445 (0.06 cases per 100 patient-years) Enbrel-treated patients versus 0 among 2890 (0%) control patients (duration of controlled treatment ranged from 3 to 48 months).

Among 15,401 patients treated with Enbrel in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of leukemia was 0.03 cases per 100 patient-years.

Other Malignancies
Information is available from 10,953 adult patients with 17,123 patient-years and 696 pediatric patients with 1282 patient-years of experience across 45 Enbrel clinical studies.

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure-adjusted rates between the Enbrel and control arms in the controlled portions of clinical studies for all indications. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general U.S. population based on the SEER database and suggests no increase in rates over time. Whether treatment with Enbrel might influence the development and course of malignancies in adults is unknown.

Melanoma and Non-melanoma skin cancer (NMSC)
Melanoma and non-melanoma skin cancer has been reported in patients treated with TNF antagonists including etanercept.

Among 15,401 patients treated with Enbrel in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of melanoma was 0.043 cases per 100 patient-years.

Among 3306 adult rheumatology (RA, PsA, AS) patients treated with Enbrel in controlled clinical trials representing approximately 2669 patient-years of therapy, the observed rate of NMSC was 0.41 cases per 100 patient-years vs 0.37 cases per 100 patient-years among 1521 control-treated patients representing 1077 patient-years. Among 1245 adult psoriasis patients treated with Enbrel in controlled clinical trials, representing approximately 283 patient-years of therapy, the observed rate of NMSC was 3.54 cases per 100 patient-years vs 1.28 cases per 100 patient-years among 720 control-treated patients representing 156 patient-years.

Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel.

Periodic skin examinations should be considered for all patients at increased risk for skin cancer.

Pediatric Patients
Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy at ≤ 18 years of age), including Enbrel. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of

30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

In clinical trials of 696 patients representing 1282 patient-years of therapy, no malignancies, including lymphoma or NMSC, have been reported.

Postmarketing Use
In global postmarketing adult and pediatric use, lymphoma and other malignancies have been reported.

5.4 Patients With Heart Failure

Two clinical trials evaluating the use of Enbrel in the treatment of heart failure were terminated early due to lack of efficacy. One of these studies suggested higher mortality in Enbrel-treated patients compared to placebo *[see Adverse Reactions (6.2)]*. There have been postmarketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known preexisting cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using Enbrel in patients who also have heart failure, and monitor patients carefully.

5.5 Hematologic Events

Rare (< 0.1%) reports of pancytopenia, including very rare (< 0.01%) reports of aplastic anemia, some with a fatal outcome, have been reported in patients treated with Enbrel. The causal relationship to Enbrel therapy remains unclear. Although no high-risk group has been identified, caution should be exercised in patients being treated with Enbrel who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (eg, persistent fever, bruising, bleeding, pallor) while on Enbrel. Discontinuation of Enbrel therapy should be considered in patients with confirmed significant hematologic abnormalities.

Two percent of patients treated concurrently with Enbrel and anakinra developed neutropenia (ANC < 1 x 10^9/L). While neutropenic, one patient developed cellulitis that resolved with antibiotic therapy.

5.6 Hepatitis B Virus Reactivation

Use of TNF-blocking agents has been associated with reactivation of hepatitis B virus (HBV), including very rare cases (< 0.01%) with Enbrel, in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with Enbrel should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, consideration should be given to stopping Enbrel and initiating anti-viral therapy with appropriate supportive treatment. The safety of resuming Enbrel therapy after HBV reactivation is controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

5.7 Allergic Reactions

Allergic reactions associated with administration of Enbrel during clinical trials have been reported in < 2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Enbrel should be discontinued immediately and appropriate therapy initiated.

Caution: The needle cap on the prefilled syringe and on the SureClick autoinjector contains dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex.

5.8 Immunizations

Live vaccines should not be given concurrently with Enbrel. It is recommended that pediatric patients, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating Enbrel therapy *[see Drug Interactions (7.1)]*.

5.9 Autoimmunity

Treatment with Enbrel may result in the formation of autoantibodies *[see Adverse Reactions (6.1)]* and, rarely (< 0.1%), in the development of a lupus-like syndrome or autoimmune hepatitis *[see Adverse Reactions (6.2)]*, which may resolve following withdrawal of Enbrel. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with Enbrel, treatment should be discontinued and the patient should be carefully evaluated.

5.10 Immunosuppression

TNF mediates inflammation and modulates cellular immune responses. TNF-blocking agents, including Enbrel, affect host defenses against infections. The effect of TNF inhibition on the development and course of malignancies is not fully understood. In a study of 49 patients with RA treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations *[see Warnings and Precautions (5.1, 5.3) and Adverse Reactions (6.1)]*.

5.11 Use in Wegener's Granulomatosis Patients

The use of Enbrel in patients with Wegener's granulomatosis receiving immunosuppressive agents is not recommended. In a study of patients with Wegener's granulomatosis, the addition of Enbrel to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies and was not associated with improved clinical outcomes when compared with standard therapy alone *[see Drug Interactions (7.3)]*.

5.12 Use with Anakinra or Abatacept

Use of Enbrel with anakinra or abatacept is not recommended *[see Drug Interactions (7.2)]*.

5.13 Use in Patients with Moderate to Severe Alcoholic Hepatitis

In a study of 48 hospitalized patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, the mortality rate in patients treated with Enbrel was similar to patients treated with placebo at 1 month but significantly higher after 6 months. Physicians should use caution when using Enbrel in patients with moderate to severe alcoholic hepatitis.

6 ADVERSE REACTIONS

Across clinical studies and postmarketing experience, the most serious adverse reactions with Enbrel were infections, neurologic events, CHF, and hematologic events *[see Warnings and Precautions (5)]*. The most common adverse reactions with Enbrel were infections and injection site reactions.

6.1 Clinical Studies Experience

Adverse Reactions in Adult Patients with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, or Plaque Psoriasis

The data described below reflect exposure to Enbrel in 2219 adult patients with RA followed for up to 80 months, in 182 patients with PsA for up to 24 months, in 138 patients with AS for up to 6 months, and in 1204 adult patients

with PsO for up to 18 months.

In controlled trials, the proportion of Enbrel-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied.

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in clinical practice.

Infections
Infections, including viral, bacterial, and fungal infections, have been observed in adult and pediatric patients. Infections have been noted in all body systems and have been reported in patients receiving Enbrel alone or in combination with other immunosuppressive agents.

In controlled portions of trials, the types and severity of infection were similar between Enbrel and the respective control group (placebo or MTX for RA and PsA patients) in RA, PsA, AS and PsO patients. Rates of infections in RA and PsO patients are provided in Table 3 and Table 4, respectively. Infections consisted primarily of upper respiratory tract infection, sinusitis and influenza.

In controlled portions of trials in RA, PsA, AS and PsO, the rates of serious infection were similar (0.8% in placebo, 3.6% in MTX, and 1.4% in Enbrel/Enbrel + MTX-treated groups). In clinical trials in rheumatologic indications, serious infections experienced by patients have included, but are not limited to, pneumonia, cellulitis, septic arthritis, bronchitis, gastroenteritis, pyelonephritis, sepsis, abscess and osteomyelitis. In clinical trials in PsO, serious infections experienced by patients have included, but are not limited to, pneumonia, cellulitis, gastroenteritis, abscess and osteomyelitis. The rate of serious infections was not increased in open-label extension trials and was similar to that observed in Enbrel- and placebo-treated patients from controlled trials.

In 66 global clinical trials of 17,505 patients (21,015 patient-years of therapy), tuberculosis was observed in approximately 0.02% of patients. In 17,696 patients (27,169 patient-years of therapy) from 38 clinical trials and 4 cohort studies in the U.S. and Canada, tuberculosis was observed in approximately 0.006% of patients. These studies include reports of pulmonary and extrapulmonary tuberculosis *[see Warnings and Precautions (5.1)]*.

Injection Site Reactions
In placebo-controlled trials in rheumatologic indications, approximately 37% of patients treated with Enbrel developed injection site reactions. In controlled trials in patients with PsO, 15% of patients treated with Enbrel developed injection site reactions during the first 3 months of treatment. All injection site reactions were described as mild to moderate (erythema, itching, pain, swelling, bleeding, bruising) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given.

Immunogenicity
Patients with RA, PsA, AS or PsO were tested at multiple time points for antibodies to etanercept. Antibodies to the TNF receptor portion or other protein components of the Enbrel drug product were detected at least once in sera of approximately 6% of adult patients with RA, PsA, AS or PsO. These antibodies were all non-neutralizing. Results from JIA patients were similar to those seen in adult RA patients treated with Enbrel.

In PsO studies that evaluated the exposure of etanercept for up to 120 weeks, the percentage of patients testing positive at the assessed time points of 24, 48, 72 and 96 weeks ranged from 3.6% - 8.7% and were all non-neutralizing. The percentage of patients testing positive increased with an increase in the duration of study; however, the clinical significance of this finding is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The immunogenicity data of Enbrel beyond 120 weeks of exposure are unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to etanercept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed

incidence of any antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to etanercept with the incidence of antibodies to other products may be misleading.

Autoantibodies

Patients with RA had serum samples tested for autoantibodies at multiple time points. In RA Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who developed new positive ANA (titer ≥ 1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In RA Study III, no pattern of increased autoantibody development was seen in Enbrel patients compared to MTX patients *[see Warnings and Precautions (5.9)]*.

Other Adverse Reactions

Table 3 summarizes adverse reactions reported in adult RA patients. The types of adverse reactions seen in patients with PsA or AS were similar to the types of adverse reactions seen in patients with RA.

Table 3. Percent of Adult RA Patients Experiencing Adverse Reactions in Controlled Clinical Trials

	Placebo Controlled[a] (Studies I, II, and a Phase 2 Study)		**Active Controlled[b] (Study III)**	
	Placebo (N = 152)	**Enbrel[c]** (N = 349)	**MTX** (N = 217)	**Enbrel[c]** (N = 415)
Reaction	**Percent of Patients**		**Percent of Patients**	
Infection[d] (total)	39	50	86	81
Upper Respiratory Infections[e]	30	38	70	65
Non-upper Respiratory Infections	15	21	59	54
Injection Site Reactions	11	37	18	43
Diarrhea	9	8	16	16
Rash	2	3	19	13
Pruritus	1	2	5	5
Pyrexia	-	3	4	2
Urticaria	1	-	4	2
Hypersensitivity	-	-	1	1

[a] Includes data from the 6-month study in which patients received concurrent MTX therapy in both arms.
[b] Study duration of 2 years.
[c] Any dose.
[d] Includes bacterial, viral and fungal infections.
[e] Most frequent Upper Respiratory Infections were upper respiratory tract infection, sinusitis and influenza.

In placebo-controlled PsO trials, the percentages of patients reporting adverse reactions in the 50 mg twice a week dose group were similar to those observed in the 25 mg twice a week dose group or placebo group.

Table 4 summarizes adverse reactions reported in adult PsO patients from Studies I and II.

Table 4. Percent of Adult PsO Patients Experiencing Adverse Reactions in Placebo-Controlled Portions of Clinical Trials (Studies I & II)

Reaction	Placebo (N = 359)	Enbrel[a] (N = 876)
	Percent of Patients	
Infection[b] (total)	28	27
Non-upper Respiratory Infections	14	12
Upper Respiratory Infections[c]	17	17
Injection Site Reactions	6	15
Diarrhea	2	3
Rash	1	1
Pruritus	2	1
Urticaria	-	1
Hypersensitivity	-	1
Pyrexia	1	-

[a] Includes 25 mg subcutaneous (SC) once weekly (QW), 25 mg SC twice weekly (BIW), 50 mg SC QW, and 50 mg SC BIW doses.
[b] Includes bacterial, viral and fungal infections.
[c] Most frequent Upper Respiratory Infections were upper respiratory tract infection, nasopharyngitis and sinusitis.

Adverse Reactions in Pediatric Patients

In general, the adverse reactions in pediatric patients were similar in frequency and type as those seen in adult patients *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Studies (14.2)]*. The types of infections reported in pediatric patients were generally mild and consistent with those commonly seen in the general pediatric population. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae.

In open-label clinical studies of children with JIA, adverse reactions reported in those ages 2 to 4 years were similar to adverse reactions reported in older children.

6.2 Postmarketing Experience

Adverse reactions have been reported during post approval use of Enbrel in adults and pediatric patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Enbrel exposure.

Adverse reactions are listed by body system below:

Blood and lymphatic system disorders:	pancytopenia, anemia, leukopenia, neutropenia, thrombocytopenia, lymphadenopathy, aplastic anemia *[see Warnings and Precautions (5.5)]*
Cardiac disorders:	congestive heart failure *[see Warnings and Precautions (5.4)]*
Gastrointestinal disorders:	inflammatory bowel disease (IBD)
General disorders:	angioedema, chest pain
Hepatobiliary disorders:	autoimmune hepatitis, elevated transaminases
Immune disorders:	macrophage activation syndrome, systemic vasculitis, sarcoidosis
Musculoskeletal and connective tissue disorders:	lupus-like syndrome

Neoplasms benign, malignant, and unspecified:	melanoma and non-melanoma skin cancers, Merkel cell carcinoma *[see Warnings and Precautions (5.3)]*
Nervous system disorders:	convulsions, multiple sclerosis, demyelination, optic neuritis, transverse myelitis, paresthesias *[see Warnings and Precautions (5.2)]*
Ocular disorders:	uveitis, scleritis
Respiratory, thoracic and mediastinal disorders:	interstitial lung disease
Skin and subcutaneous tissue disorders:	cutaneous lupus erythematosus, cutaneous vasculitis (including leukocytoclastic vasculitis), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, subcutaneous nodule, new or worsening psoriasis (all sub-types including pustular and palmoplantar)

Opportunistic infections, including atypical mycobacterial infection, herpes zoster, aspergillosis and *Pneumocystis jiroveci* pneumonia, and protozoal infections have also been reported in postmarketing use.

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with Enbrel.

7.1 Vaccines

Most PsA patients receiving Enbrel were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had 2-fold rises in titers compared to patients not receiving Enbrel. The clinical significance of this is unknown. Patients receiving Enbrel may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel.

Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with varicella zoster immune globulin *[see Warnings and Precautions (5.8, 5.10)]*.

7.2 Immune-Modulating Biologic Products

In a study in which patients with active RA were treated for up to 24 weeks with concurrent Enbrel and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with Enbrel alone (0%) *[see Warnings and Precautions (5.12)]* and did not result in higher ACR response rates compared to Enbrel alone. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure. Two percent of patients treated concurrently with Enbrel and anakinra developed neutropenia (ANC $< 1 \times 10^9$/L).

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events, including infections, and did not demonstrate increased clinical benefit *[see Warnings and Precautions (5.12)]*.

7.3 Cyclophosphamide

The use of Enbrel in patients receiving concurrent cyclophosphamide therapy is not recommended *[see Warnings and Precautions (5.11)]*.

7.4 Sulfasalazine

Patients in a clinical study who were on established therapy with sulfasalazine, to which Enbrel was added, were

noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either Enbrel or sulfasalazine alone. The clinical significance of this observation is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to Enbrel. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to Enbrel, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether Enbrel is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Enbrel, a decision should be made whether to discontinue nursing or to discontinue the drug.

8.4 Pediatric Use

Enbrel is indicated for treatment of polyarticular JIA in patients ages 2 years and older *[see Indications and Usage (1.2), Dosage and Administration (2.3), Warnings and Precautions (5.8), Adverse Reactions (6), and Clinical Studies (14.2)]*.

Enbrel has not been studied in children < 2 years of age with JIA. The safety and efficacy of Enbrel in pediatric patients with PsO have not been studied.

Rare (< 0.1%) cases of IBD have been reported in JIA patients receiving Enbrel, which is not effective for the treatment of IBD *[see Adverse Reactions (6.2)]*.

8.5 Geriatric Use

A total of 480 RA patients ages 65 years or older have been studied in clinical trials. In PsO randomized clinical trials, a total of 138 out of 1965 patients treated with Enbrel or placebo were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but the number of geriatric PsO patients is too small to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

8.6 Use in Diabetics

There have been reports of hypoglycemia following initiation of Enbrel therapy in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

10 OVERDOSAGE

Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of Enbrel. Single IV doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

11 DESCRIPTION

Enbrel (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

The solution of Enbrel in the single-use prefilled syringe and the single-use prefilled SureClick autoinjector is clear and colorless, sterile, preservative-free, and is formulated at pH 6.3 ± 0.2.

Enbrel is also supplied in a multiple-use vial as a sterile, white, preservative-free, lyophilized powder. Reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colorless solution with a pH of 7.4 ± 0.3.

Table 5. Contents of Enbrel

Presentation	Active Ingredient Content	Inactive Ingredients Content
Enbrel 50 mg prefilled syringe and SureClick autoinjector	0.98 mL of a 50 mg/mL solution of etanercept	1% sucrose 100 mM sodium chloride 25 mM L-arginine hydrochloride 25 mM sodium phosphate
Enbrel 25 mg prefilled syringe	0.51 mL of a 50 mg/mL solution of etanercept	1% sucrose 100 mM sodium chloride 25 mM L-arginine hydrochloride 25 mM sodium phosphate
Enbrel 25 mg multiple-use vial	25 mg etanercept	40 mg mannitol 10 mg sucrose 1.2 mg tromethamine

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive. In *in vitro* studies, large complexes of etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds Enbrel) are not lysed in the presence or absence of complement.

12.2 Pharmacodynamics

Etanercept can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (eg, E-selectin, and to a lesser extent, intercellular adhesion

molecule-1 [ICAM-1]), serum levels of cytokines (eg, IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin). Etanercept has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.

12.3 Pharmacokinetics

After administration of 25 mg of Enbrel by a single SC injection to 25 patients with RA, a mean ± standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (C_{max}) of 1.1 ± 0.6 mcg/mL and time to C_{max} of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean C_{max} was 2.4 ± 1.0 mcg/mL (N = 23). Patients exhibited a 2- to 7-fold increase in peak serum concentrations and approximately 4-fold increase in $AUC_{0\text{-}72\ hr}$ (range 1- to 17-fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months. The pharmacokinetic parameters in patients with PsO were similar to those seen in patients with RA.

In another study, serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg Enbrel once weekly and those treated with 25 mg Enbrel twice weekly. The mean (± standard deviation) C_{max}, C_{min}, and partial AUC were 2.4 ± 1.5 mcg/mL, 1.2 ± 0.7 mcg/mL, and 297 ± 166 mcg•h/mL, respectively, for patients treated with 50 mg Enbrel once weekly (N = 21); and 2.6 ± 1.2 mcg/mL, 1.4 ± 0.7 mcg/mL, and 316 ± 135 mcg•h/mL for patients treated with 25 mg Enbrel twice weekly (N = 16).

Patients with JIA (ages 4 to 17 years) were administered 0.4 mg/kg of Enbrel twice weekly (up to a maximum dose of 50 mg per week) for up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Limited data suggest that the clearance of etanercept is reduced slightly in children ages 4 to 8 years. Population pharmacokinetic analyses predict that the pharmacokinetic differences between the regimens of 0.4 mg/kg twice weekly and 0.8 mg/kg once weekly in JIA patients are of the same magnitude as the differences observed between twice weekly and weekly regimens in adult RA patients.

In clinical studies with Enbrel, pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. The pharmacokinetics of etanercept were unaltered by concomitant MTX in RA patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on etanercept disposition.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept or its effect on fertility. Mutagenesis studies were conducted *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

The safety and efficacy of Enbrel were assessed in four randomized, double-blind, controlled studies. The results of all four trials were expressed in percentage of patients with improvement in RA using ACR response criteria.

Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs) (eg, hydroxychloroquine, oral or injectable gold, MTX, azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr, C-reactive protein (CRP) > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg Enbrel or placebo were administered SC twice a week for 6 consecutive months.

Study II evaluated 89 patients and had similar inclusion criteria to Study I except that patients in Study II had additionally received MTX for at least 6 months with a stable dose (12.5 to 25 mg/week) for at least 4 weeks and they had at least 6 tender or painful joints. Patients in Study II received a dose of 25 mg Enbrel or placebo SC twice a week for 6 months in addition to their stable MTX dose.

Study III compared the efficacy of Enbrel to MTX in patients with active RA. This study evaluated 632 patients who were ≥ 18 years old with early (² 3 years disease duration) active RA, had never received treatment with MTX, and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg Enbrel were administered SC twice a week for 12 consecutive months. The study was unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of therapy. The majority of patients remained in the study on the treatment to which they were randomized through 2 years, after which they entered an extension study and received open-label 25 mg Enbrel. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or Enbrel doses, respectively.

Study IV evaluated 682 adult patients with active RA of 6 months to 20 years duration (mean of 7 years) who had an inadequate response to at least one DMARD other than MTX. Forty-three percent of patients had previously received MTX for a mean of 2 years prior to the trial at a mean dose of 12.9 mg. Patients were excluded from this study if MTX had been discontinued for lack of efficacy or for safety considerations. The patient baseline characteristics were similar to those of patients in Study I. Patients were randomized to MTX alone (7.5 to 20 mg weekly, dose escalated as described for Study III; median dose 20 mg), Enbrel alone (25 mg twice weekly), or the combination of Enbrel and MTX initiated concurrently (at the same doses as above). The study evaluated ACR response, Sharp radiographic score, and safety.

Clinical Response

A higher percentage of patients treated with Enbrel and Enbrel in combination with MTX achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the comparison groups. The results of Studies I, II, and III are summarized in Table 6. The results of Study IV are summarized in Table 7.

Table 6. ACR Responses in Placebo- and Active-Controlled Trials (Percent of Patients)

	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
Response	Placebo N = 80	Enbrel[a] N = 78	MTX/ Placebo N = 30	MTX/Enbrel[a] N = 59	MTX N = 217	Enbrel[a] N = 207
ACR 20						
Month 3	23%	62%[b]	33%	66%[b]	56%	62%
Month 6	11%	59%[b]	27%	71%[b]	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41%[b]	0%	42%[b]	24%	29%
Month 6	5%	40%[b]	3%	39%[b]	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15%[b]	0%	15%[b]	7%	13%[c]
Month 6	1%	15%[b]	0%	15%[b]	14%	21%[c]
Month 12	NA	NA	NA	NA	22%	25%

[a] 25 mg Enbrel SC twice weekly
[b] $p < 0.01$, Enbrel vs placebo
[c] $p < 0.05$, Enbrel vs MTX

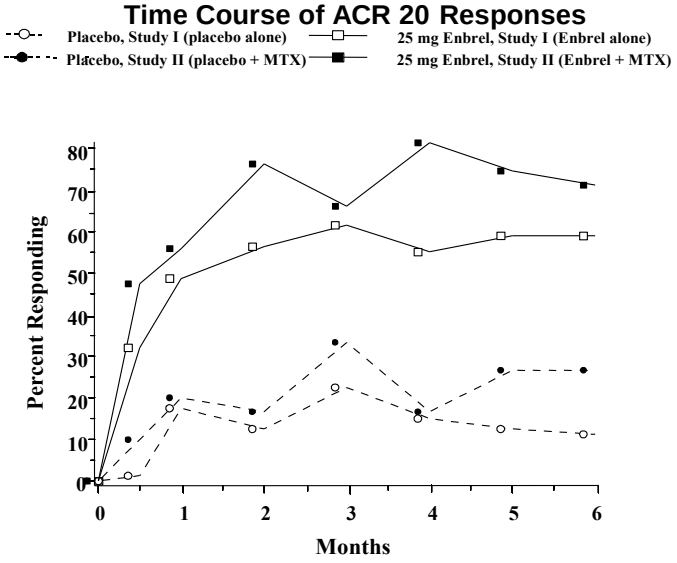
Table 7. Study IV Clinical Efficacy Results: Comparison of MTX vs Enbrel vs Enbrel in Combination With MTX in Patients With Rheumatoid Arthritis of 6 Months to 20 Years Duration (Percent of Patients)

Endpoint	MTX (N = 228)	Enbrel (N = 223)	Enbrel/MTX (N = 231)
ACR N[a, b]			
Month 12	40%	47%	63%[c]
ACR 20			
Month 12	59%	66%	75%[c]
ACR 50			
Month 12	36%	43%	63%[c]
ACR 70			
Month 12	17%	22%	40%[c]
Major Clinical Response[d]	6%	10%	24%[c]

[a] Values are medians.
[b] ACR N is the percent improvement based on the same core variables used in defining ACR 20, ACR 50, and ACR 70.
[c] $p < 0.05$ for comparisons of Enbrel/MTX vs Enbrel alone or MTX alone.
[d] Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

The time course for ACR 20 response rates for patients receiving placebo or 25 mg Enbrel in Studies I and II is summarized in Figure 1. The time course of responses to Enbrel in Study III was similar.

Figure 1:
Time Course of ACR 20 Responses



Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen in Studies I and III: 25 mg Enbrel was more effective than 10 mg (10 mg was not evaluated in Study II). Enbrel was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, ACR response rates and improvement in all the individual ACR response criteria were maintained through 24 months of Enbrel therapy. Over the 2-year study, 23% of Enbrel patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

The results of the components of the ACR response criteria for Study I are shown in Table 8. Similar results were observed for Enbrel-treated patients in Studies II and III.

Table 8. Components of ACR Response in Study I

	Placebo N = 80		Enbrel[a] N = 78	
Parameter (median)	Baseline	3 Months	Baseline	3 Months[*]
Number of tender joints [b]	34.0	29.5	31.2	10.0[f]
Number of swollen joints [c]	24.0	22.0	23.5	12.6[f]
Physician global assessment [d]	7.0	6.5	7.0	3.0[f]
Patient global assessment [d]	7.0	7.0	7.0	3.0[f]
Pain [d]	6.9	6.6	6.9	2.4[f]
Disability index [e]	1.7	1.8	1.6	1.0[f]
ESR (mm/hr)	31.0	32.0	28.0	15.5[f]
CRP (mg/dL)	2.8	3.9	3.5	0.9[f]

[*] Results at 6 months showed similar improvement.
[a] 25 mg Enbrel SC twice weekly.
[b] Scale 0-71.
[c] Scale 0-68.
[d] Visual analog scale: 0 = best; 10 = worst.
[e] Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[f] $p < 0.01$, Enbrel vs placebo, based on mean percent change from baseline.

After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Reintroduction of treatment with Enbrel after discontinuations of up to 18 months resulted in the same magnitudes of response as in patients who received Enbrel without interruption of therapy, based on results of open-label studies.

Continued durable responses were seen for over 60 months in open-label extension treatment trials when patients received Enbrel without interruption. A substantial number of patients who initially received concomitant MTX or corticosteroids were able to reduce their doses or discontinue these concomitant therapies while maintaining their clinical responses.

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the Health Assessment Questionnaire (HAQ). Additionally, in Study III, patients were administered the SF-36 Health Survey. In Studies I and II, patients treated with 25 mg Enbrel twice weekly showed greater improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison to placebo ($p < 0.001$) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I, the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the 25 mg Enbrel group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the Enbrel/MTX group and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg Enbrel twice weekly. All subdomains of the HAQ in Studies I and III were improved in patients treated with Enbrel.

In Study III, patients treated with 25 mg Enbrel twice weekly showed greater improvement from baseline in SF-36 physical component summary score compared to Enbrel 10 mg twice weekly and no worsening in the SF-36 mental component summary score. In open-label Enbrel studies, improvements in physical function and disability measures have been maintained for up to 4 years.

In Study IV, median HAQ scores improved from baseline levels of 1.8, 1.8, and 1.8 to 1.1, 1.0, and 0.6 at 12 months in the MTX, Enbrel, and Enbrel/MTX combination treatment groups, respectively (combination versus both MTX and Enbrel, $p < 0.01$). Twenty-nine percent of patients in the MTX alone treatment group had an improvement of HAQ of at least 1 unit versus 40% and 51% in the Enbrel alone and the Enbrel/MTX combination treatment groups, respectively.

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score

(TSS) and its components, the erosion score and joint space narrowing (JSN) score. Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. The results are shown in Table 9. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

Table 9. Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	25 mg Enbrel	MTX/Enbrel (95% Confidence Interval*)	P Value
12 Months	Total Sharp Score	1.59	1.00	0.59 (-0.12, 1.30)	0.1
	Erosion Score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN Score	0.56	0.52	0.04 (-0.39, 0.46)	0.5
6 Months	Total Sharp Score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion Score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN Score	0.38	0.27	0.11 (-0.14, 0.35)	0.6

* 95% confidence intervals for the differences in change scores between MTX and Enbrel.

Patients continued on the therapy to which they were randomized for the second year of Study III. Seventy-two percent of patients had x-rays obtained at 24 months. Compared to the patients in the MTX group, greater inhibition of progression in TSS and erosion score was seen in the 25 mg Enbrel group, and, in addition, less progression was noted in the JSN score.

In the open-label extension of Study III, 48% of the original patients treated with 25 mg Enbrel have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage, as measured by the TSS, and 55% of them had no progression of structural damage. Patients originally treated with MTX had further reduction in radiographic progression once they began treatment with Enbrel.

In Study IV, less radiographic progression (TSS) was observed with Enbrel in combination with MTX compared with Enbrel alone or MTX alone at month 12 (Table 10). In the MTX treatment group, 55% of patients experienced no radiographic progression (TSS change ≤ 0.0) at 12 months compared to 63% and 76% in the Enbrel alone and the Enbrel/MTX combination treatment groups, respectively.

Table 10. Mean Radiographic Change in Study IV at 12 Months (95% Confidence Interval)

	MTX (N = 212)*	Enbrel (N = 212)*	Enbrel/MTX (N = 218)*
Total Sharp Score (TSS)	2.80 (1.08, 4.51)	0.52[a] (-0.10, 1.15)	-0.54[b,c] (-1.00, -0.07)
Erosion Score (ES)	1.68 (0.61, 2.74)	0.21[a] (-0.20, 0.61)	-0.30[b] (-0.65, 0.04)
Joint Space Narrowing (JSN) Score	1.12 (0.34, 1.90)	0.32 (0.00, 0.63)	-0.23[b,c] (-0.45, -0.02)

* Analyzed radiographic ITT population.
[a] $p < 0.05$ for comparison of Enbrel vs MTX.
[b] $p < 0.05$ for comparison of Enbrel/MTX vs MTX.
[c] $p < 0.05$ for comparison of Enbrel/MTX vs Enbrel.

Once Weekly Dosing
The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. Fifty-three patients received placebo, 214 patients received 50 mg Enbrel once weekly, and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment groups were similar.

14.2 Polyarticular Juvenile Idiopathic Arthritis (JIA)

The safety and efficacy of Enbrel were assessed in a 2-part study in 69 children with polyarticular JIA who had a variety of JIA onset types. Patients ages 2 to 17 years with moderately to severely active polyarticular JIA refractory to or intolerant of MTX were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on Enbrel or receive placebo for 4 months and assessed for disease flare. Responses were measured using the JIA Definition of Improvement (DOI), defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of the six JIA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a ≥ 30% worsening in three of the six JIA core set criteria and ≥ 30% improvement in not more than one of the six JIA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Each component of the JIA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on Enbrel. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JIA patients who developed a disease flare in part 2 and reintroduced Enbrel treatment up to 4 months after discontinuation re-responded to Enbrel therapy in open-label studies. Most of the responding patients who continued Enbrel therapy without interruption have maintained responses for up to 48 months.

Studies have not been done in patients with polyarticular JIA to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy, or to assess the combination of Enbrel with MTX.

14.3 Psoriatic Arthritis

The safety and efficacy of Enbrel were assessed in a randomized, double-blind, placebo-controlled study in 205 patients with PsA. Patients were between 18 and 70 years of age and had active PsA (≥ 3 swollen joints and ≥ 3 tender joints) in one or more of the following forms: (1) distal interphalangeal (DIP) involvement (N = 104); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis; N = 173); (3) arthritis mutilans (N = 3); (4) asymmetric psoriatic arthritis (N = 81); or (5) ankylosing spondylitis-like (N = 7). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients on MTX therapy at enrollment (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week MTX. Doses of 25 mg Enbrel or placebo were administered SC twice a week during the initial 6-month double-blind period of the study. Patients continued to receive blinded therapy in an up to 6-month maintenance period until all patients had completed the controlled period. Following this, patients received open-label 25 mg Enbrel twice a week in a 12-month extension period.

Compared to placebo, treatment with Enbrel resulted in significant improvements in measures of disease activity (Table 11).

Table 11. Components of Disease Activity in Psoriatic Arthritis

	Placebo N = 104		Enbrel[a] N = 101	
Parameter (median)	Baseline	6 Months	Baseline	6 Months
Number of tender joints[b]	17.0	13.0	18.0	5.0
Number of swollen joints[c]	12.5	9.5	13.0	5.0
Physician global assessment[d]	3.0	3.0	3.0	1.0
Patient global assessment[d]	3.0	3.0	3.0	1.0
Morning stiffness (minutes)	60	60	60	15
Pain[d]	3.0	3.0	3.0	1.0
Disability index[e]	1.0	0.9	1.1	0.3
CRP (mg/dL)[f]	1.1	1.1	1.6	0.2

[a] $p < 0.001$ for all comparisons between Enbrel and placebo at 6 months.
[b] Scale 0-78.
[c] Scale 0-76.
[d] Likert scale: 0 = best; 5 = worst.
[e] Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[f] Normal range: 0-0.79 mg/dL.

Among patients with PsA who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and 9%, respectively, of patients receiving Enbrel, compared to 13%, 4%, and 1%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of PsA, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. The results of this study were similar to those seen in an earlier single-center, randomized, placebo-controlled study of 60 patients with PsA.

The skin lesions of psoriasis were also improved with Enbrel, relative to placebo, as measured by percentages of patients achieving improvements in the Psoriasis Area and Severity Index (PASI). Responses increased over time, and at 6 months, the proportions of patients achieving a 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the Enbrel group (N = 66), compared to 18% and 3%, respectively, in the placebo group (N = 62). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Radiographic Response

Radiographic changes were also assessed in the PsA study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. A modified Total Sharp Score (TSS), which included distal interphalangeal joints (ie, not identical to the modified TSS used for RA) was used by readers blinded to treatment group to assess the radiographs. Some radiographic features specific to PsA (eg, pencil-and-cup deformity, joint space widening, gross osteolysis, and ankylosis) were included in the scoring system, but others (eg, phalangeal tuft resorption, juxta-articular and shaft periostitis) were not.

Most patients showed little or no change in the modified TSS during this 24-month study (median change of 0 in both patients who initially received Enbrel or placebo). More placebo-treated patients experienced larger magnitudes of radiographic worsening (increased TSS) compared to Enbrel treatment during the controlled period of the study. At 12 months, in an exploratory analysis, 12% (12 of 104) of placebo patients compared to none of the 101 Enbrel-treated patients had increases of 3 points or more in TSS. Inhibition of radiographic progression was maintained in patients who continued on Enbrel during the second year. Of the patients with 1-year and 2-year x-rays, 3% (2 of 71) had increases of 3 points or more in TSS at 1 and 2 years.

Physical Function Response

In the PsA study, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 25 mg Enbrel twice weekly showed greater improvement from baseline in the HAQ-DI score (mean decreases of 54% at both months 3 and 6) in comparison to placebo (mean decreases of 6% at both months 3 and 6) ($p < 0.001$). At months 3 and 6, patients treated with Enbrel showed greater improvement from baseline in the SF-36 physical component summary score compared to patients treated with

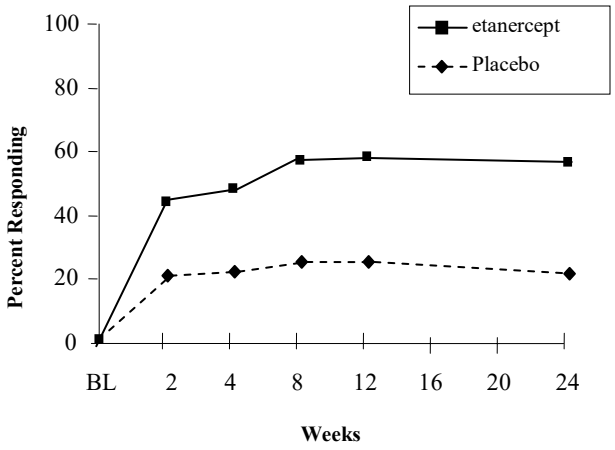
placebo, and no worsening in the SF-36 mental component summary score. Improvements in physical function and disability measures were maintained for up to 2 years through the open-label portion of the study.

14.4 Ankylosing Spondylitis

The safety and efficacy of Enbrel were assessed in a randomized, double-blind, placebo-controlled study in 277 patients with active AS. Patients were between 18 and 70 years of age and had AS as defined by the modified New York Criteria for Ankylosing Spondylitis. Patients were to have evidence of active disease based on values of ≥ 30 on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness duration and intensity, and two of the following three other parameters: a) patient global assessment, b) average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate, or prednisone (≤ 10 mg/day) could continue these drugs at stable doses for the duration of the study. Doses of 25 mg Enbrel or placebo were administered SC twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Compared to placebo, treatment with Enbrel resulted in improvements in the ASAS and other measures of disease activity (Figure 2 and Table 12).

Figure 2. ASAS 20 Responses in Ankylosing Spondylitis



At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of patients receiving Enbrel, compared to 27%, 13%, and 7%, respectively, of patients receiving placebo ($p \leq 0.0001$, Enbrel vs placebo). Similar responses were seen at week 24. Responses were similar between those patients receiving concomitant therapies at baseline and those who were not. The results of this study were similar to those seen in a single-center, randomized, placebo-controlled study of 40 patients and a multicenter, randomized, placebo-controlled study of 84 patients with AS.

Table 12. Components of Ankylosing Spondylitis Disease Activity

	Placebo N = 139		Enbrel[a] N = 138	
Median values at time points	Baseline	6 Months	Baseline	6 Months
ASAS response criteria				
Patient global assessment [b]	63	56	63	36
Back pain [c]	62	56	60	34
BASFI [d]	56	55	52	36
Inflammation [e]	64	57	61	33
Acute phase reactants				
CRP (mg/dL) [f]	2.0	1.9	1.9	0.6
Spinal mobility (cm):				
Modified Schober's test	3.0	2.9	3.1	3.3
Chest expansion	3.2	3.0	3.3	3.9
Occiput-to-wall measurement	5.3	6.0	5.6	4.5

[a] $p < 0.0015$ for all comparisons between Enbrel and placebo at 6 months. P values for continuous endpoints were based on percent change from baseline.

[b] Measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe."

[c] Average of total nocturnal and back pain scores, measured on a VAS with 0 = "no pain" and 100 = "most severe pain."

[d] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.

[e] Inflammation represented by the average of the last 2 questions on the 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

[f] C-reactive protein (CRP) normal range: 0-1.0 mg/dL.

14.5 Plaque Psoriasis

The safety and efficacy of Enbrel were assessed in two randomized, double-blind, placebo-controlled studies in adults with chronic stable PsO involving ≥ 10% of the body surface area, a minimum Psoriasis Area and Severity Index (PASI) score of 10 and who had received or were candidates for systemic antipsoriatic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis and patients with severe infections within 4 weeks of screening were excluded from study. No concomitant major antipsoriatic therapies were allowed during the study.

Study I evaluated 672 patients who received placebo or Enbrel SC at doses of 25 mg once a week, 25 mg twice a week, or 50 mg twice a week for 3 months. After 3 months, patients continued on blinded treatments for an additional 3 months during which time patients originally randomized to placebo began treatment with blinded Enbrel at 25 mg twice weekly (designated as placebo/Enbrel in Table 13); patients originally randomized to Enbrel continued on the originally randomized dose (designated as Enbrel/Enbrel groups in Table 13).

Study II evaluated 611 patients who received placebo or Enbrel SC at doses of 25 mg or 50 mg twice a week for 3 months. After 3 months of randomized, blinded treatment, patients in all three arms began receiving open-label Enbrel at 25 mg twice weekly for 9 additional months.

Response to treatment in both studies was assessed after 3 months of therapy and was defined as the proportion of patients who achieved a reduction in PASI score of at least 75% from baseline. The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling).

Other evaluated outcomes included the proportion of patients who achieved a score of "clear" or "minimal" by the Static Physician Global Assessment (sPGA) and the proportion of patients with a reduction of PASI of at least 50% from baseline. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = none" indicating the physician's overall assessment of the PsO severity focusing on induration, erythema and scaling. Treatment success of "clear"

or "minimal" consisted of none or minimal elevation in plaque, up to faint red coloration in erythema and none or minimal fine scale over < 5% of the plaque.

Patients in all treatment groups and in both studies had a median baseline PASI score ranging from 15 to 17, and the percentage of patients with baseline sPGA classifications ranged from 54% to 66% for moderate, 17% to 26% for marked and 1% to 5% for severe. Across all treatment groups, the percentage of patients who previously received systemic therapy for PsO ranged from 61% to 65% in Study I and 71% to 75% in Study II, and those who previously received phototherapy ranged from 44% to 50% in Study I and 72% to 73% in Study II.

More patients randomized to Enbrel than placebo achieved at least a 75% reduction from baseline PASI score (PASI 75) with a dose response relationship across doses of 25 mg once a week, 25 mg twice a week and 50 mg twice a week (Tables 13 and 14). The individual components of the PASI (induration, erythema and scaling) contributed comparably to the overall treatment-associated improvement in PASI.

Table 13. Study I Outcomes at 3 and 6 Months

		Enbrel/Enbrel		
	Placebo/Enbrel 25 mg BIW (N = 168)	25 mg QW (N = 169)	25 mg BIW (N = 167)	50 mg BIW (N = 168)
3 Months				
PASI 75 n (%)	6 (4%)	23 (14%)[a]	53 (32%)[b]	79 (47%)[b]
Difference (95% CI)		10% (4, 16)	28% (21, 36)	43% (35, 52)
sPGA, "clear" or "minimal" n (%)	8 (5%)	36 (21%)[b]	53 (32%)[b]	79 (47%)[b]
Difference (95% CI)		17% (10, 24)	27% (19, 35)	42% (34, 50)
PASI 50 n (%)	24 (14%)	62 (37%)[b]	90 (54%)[b]	119 (71%)[b]
Difference (95% CI)		22% (13, 31)	40% (30, 49)	57% (48, 65)
6 Months				
PASI 75 n (%)	55 (33%)	36 (21%)	68 (41%)	90 (54%)

[a] p = 0.001 compared with placebo.
[b] p < 0.0001 compared with placebo.

Table 14. Study II Outcomes at 3 Months

		Enbrel	
	Placebo (N = 204)	25 mg BIW (N = 204)	50 mg BIW (N = 203)
PASI 75 n (%)	6 (3%)	66 (32%)[a]	94 (46%)[a]
Difference (95% CI)		29% (23, 36)	43% (36, 51)
sPGA, "clear" or "minimal" n (%)	7 (3%)	75 (37%)[a]	109 (54%)[a]
Difference (95% CI)		34% (26, 41)	50% (43, 58)
PASI 50 n (%)	18 (9%)	124 (61%)[a]	147 (72%)[a]
Difference (95% CI)		52% (44, 60)	64% (56, 71)

[a] p < 0.0001 compared with placebo.

Among PASI 75 achievers in both studies, the median time to PASI 50 and PASI 75 was approximately 1 month and approximately 2 months, respectively, after the start of therapy with either 25 or 50 mg twice a week.

In Study I, patients who achieved PASI 75 at month 6 were entered into a study drug withdrawal and retreatment period. Following withdrawal of study drug, these patients had a median duration of PASI 75 of between 1 and 2 months.

In Study I, among patients who were PASI 75 responders at 3 months, retreatment with their original blinded Enbrel dose after discontinuation of up to 5 months resulted in a similar proportion of responders as in the initial double-blind portion of the study.

In Study II, most patients initially randomized to 50 mg twice a week continued in the study after month 3 and had their Enbrel dose decreased to 25 mg twice a week. Of the 91 patients who were PASI 75 responders at month 3, 70 (77%) maintained their PASI 75 response at month 6.

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 13 Registries, 1992-2002.

16 HOW SUPPLIED/STORAGE AND HANDLING

Administration of one 50 mg Enbrel prefilled syringe or one Enbrel SureClick autoinjector provides a dose equivalent to two 25 mg Enbrel prefilled syringes or two multiple-use vials of lyophilized Enbrel, when vials are reconstituted and administered as recommended.

16.1 Enbrel Single-use Prefilled Syringe and Enbrel Single-use Prefilled SureClick Autoinjector

Each Enbrel single-use prefilled syringe and Enbrel single-use prefilled SureClick autoinjector contains 50 mg/mL of etanercept in a single-dose syringe with a 27-gauge, ½-inch needle.

50 mg single-use prefilled syringe	Carton of 4	NDC 58406-435-04
50 mg single-use prefilled SureClick autoinjector	Carton of 4	NDC 58406-445-04
25 mg single-use prefilled syringe	Carton of 4	NDC 58406-455-04

Do not use Enbrel beyond the expiration date stamped on the carton or barrel label. Enbrel must be refrigerated at 2° to 8°C (36° to 46°F). DO NOT FREEZE. Keep the product in the original carton to protect from light until the time of use. Do not shake.

16.2 Enbrel Multiple-use Vial (Recommended for Weight-based Dosing)

Enbrel multiple-use vial is supplied in a carton containing four dose trays. Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge ½-inch needle, one vial adapter, and one plunger. Each carton contains four “Mixing Date:” stickers.

25 mg multiple-use vial	Carton of 4	NDC 58406-425-34

Do not use a dose tray beyond the expiration date stamped on the dose tray label. The dose tray containing Enbrel (sterile powder) must be refrigerated at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Patients or their caregivers should be provided the Enbrel "Medication Guide" and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

17.1 Patient Counseling

Patients should be advised of the potential benefits and risks of Enbrel. Physicians should instruct their patients to read the Medication Guide before starting Enbrel therapy and to reread each time the prescription is renewed.

Infections
Inform patients that Enbrel may lower the ability of their immune system to fight infections. Advise patients of the importance of contacting their doctor if they develop any symptoms of infection, tuberculosis or reactivation of hepatitis B virus infections.

Other Medical Conditions
Advise patients to report any signs of new or worsening medical conditions, such as central nervous system demyelinating disorders, heart failure or autoimmune disorders, such as lupus-like syndrome or autoimmune hepatitis. Counsel about the risk of lymphoma and other malignancies while receiving Enbrel. Advise patients to report any symptoms suggestive of a pancytopenia, such as bruising, bleeding, persistent fever or pallor.

Allergic Reactions
Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe and SureClick autoinjector contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

17.2 Administration of Enbrel

If a patient or caregiver is to administer Enbrel, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose [see the Enbrel (etanercept) "Instructions for Use" insert]. The first injection should be performed under the supervision of a qualified healthcare professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique, as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes.

A puncture-resistant container for disposal of needles, syringes and autoinjectors should be used. If the product is intended for multiple use, additional syringes, needles and alcohol swabs will be required.

Patients can be advised to call 1-888-4ENBREL (1-888-436-2735) or visit www.enbrel.com for more information about Enbrel.

Enbrel® (etanercept)

Manufactured by:
Immunex Corporation
Thousand Oaks, CA 91320-1799
U.S. License Number 1132
Marketed by Amgen Inc. and Pfizer Inc.

Footnote 6

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIPITOR safely and effectively. See full prescribing information for LIPITOR.

LIPITOR® (atorvastatin calcium) Tablets for oral administration
Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------
LIPITOR is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use
LIPITOR has not been studied in *Fredrickson* Types I and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------
Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
10, 20, 40, and 80 mg tablets (3).

----------CONTRAINDICATIONS----------
Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who are pregnant or may become pregnant (4.3).
Nursing mothers (4.4).
Hypersensitivity to any component of this medication (4.2).

----------WARNINGS AND PRECAUTIONS----------
Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine, fibrates, and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. In cases of myopathy or rhabdomyolysis, therapy should be temporarily withheld or discontinued (5.1).

Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the LIPITOR 80 mg group vs. placebo (5.5).

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with LIPITOR in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at (1-800-438-1985 and www.pfizer.com) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20 mg atorvastatin daily. The lowest dose necessary should be used.

- Digoxin: Patients should be monitored appropriately (7.5).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.6).
- Rifampin should be simultaneously co-administered with LIPITOR (7.4).

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION
Revised: [6/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, LIPITOR can be started simultaneously with diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, LIPITOR is indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

1.2 Hyperlipidemia

LIPITOR is indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels *(Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥ 190 mg/dL or
  b. LDL-C remains ≥ 160 mg/dL and:
    - there is a positive family history of premature cardiovascular disease or
    - two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

LIPITOR has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons *(Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. LIPITOR can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response (see current *NCEP Guidelines*). After initiation and/or upon titration of LIPITOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of LIPITOR is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of LIPITOR in patients with homozygous FH is 10 to 80 mg daily. LIPITOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

LIPITOR may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see *Warnings and Precautions*, *Skeletal Muscle (5.1), Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of LIPITOR; thus, dosage adjustment in patients with renal dysfunction is not necessary [see *Warnings and Precautions, Skeletal Muscle (5.1), Clinical Pharmacology, Pharmacokinetics (12.3)*].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir

In patients taking cyclosporine, therapy should be limited to LIPITOR 10 mg once daily. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, for doses of LIPITOR exceeding 20 mg, appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, elliptical, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. LIPITOR may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of LIPITOR use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. LIPITOR SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this

drug, LIPITOR should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mothers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require LIPITOR treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with LIPITOR and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6), Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20mg atorvastatin daily. The lowest dose necessary should be used.

LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in**

0.7% of patients who received LIPITOR in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of LIPITOR.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with LIPITOR. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of LIPITOR is recommended.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of LIPITOR [see *Contraindications (4.1)*].

5.3 Endocrine Function

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that LIPITOR does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where LIPITOR 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:
Rhabdomyolysis and myopathy [see *Warnings and Precautions (5.1)*]
Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the LIPITOR placebo-controlled clinical trial database of 16,066 patients (8755 LIPITOR vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on LIPITOR and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with LIPITOR that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with LIPITOR in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with LIPITOR (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patents treated with any dose of LIPITOR and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse Reaction ≥ 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include:
Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system:* epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40–80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with LIPITOR 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with LIPITOR was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39–77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with LIPITOR 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)
In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29–78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with LIPITOR 10 mg daily (n=5006) or LIPITOR 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4–10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)
In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26–80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with LIPITOR 80 mg/day (n=4439) or simvastatin 20–40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In SPARCL involving 4731 subjects (age range 21–92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with LIPITOR 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4–10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, LIPITOR 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 LIPITOR vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) LIPITOR vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the LIPITOR 80 mg/day group vs. 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the LIPITOR 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the LIPITOR 80 mg group (5.0%) than in the placebo group (4.0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LIPITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with LIPITOR therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, hepatic failure, dizziness, memory impairment, depression, and peripheral neuropathy.

6.3 Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4: LIPITOR is metabolized by cytochrome P450 3A4. Concomitant administration of LIPITOR with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 80 mg with clarithromycin (500 mg twice daily) compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the LIPITOR dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 40 mg with ritonavir plus saquinavir (400 mg twice daily) or LIPITOR 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking HIV protease inhibitors, caution should be used when the LIPITOR dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when the LIPITOR dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*]. In cases where co-administration of LIPITOR with cyclosporine is necessary, the dose of LIPITOR should not exceed 10 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Rifampin or other Inducers of Cytochrome P450 3A4: Concomitant administration of LIPITOR with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of LIPITOR with rifampin is recommended, as delayed administration of LIPITOR after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.5 Digoxin: When multiple doses of LIPITOR and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

7.6 Oral Contraceptives: Co-administration of LIPITOR and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see *Clinical Pharmacology (12.3)*]. These increases should be considered when selecting an oral contraceptive for a woman taking LIPITOR.

7.7 Warfarin: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

LIPITOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate

expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2) [see *Contraindications, Pregnancy (4.3)*].

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. LIPITOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPITOR, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring LIPITOR treatment should be advised not to nurse their infants [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with LIPITOR had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10-17 years) (6.3)*; and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age) (2.2*)]. Adolescent females should be counseled on appropriate contraceptive methods while on LIPITOR therapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies*, *Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of the 39,828 patients who received LIPITOR in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, LIPITOR should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

Lipitor is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

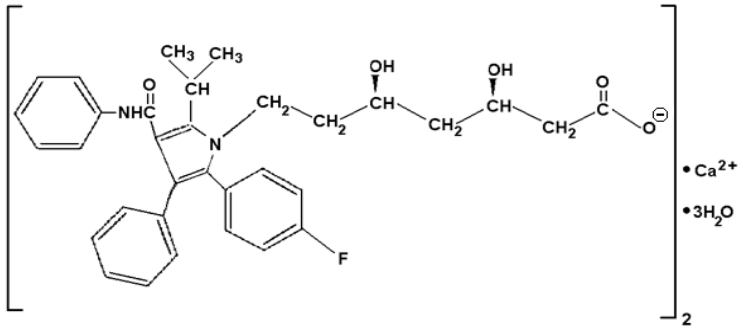
10 OVERDOSAGE

There is no specific treatment for LIPITOR overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance LIPITOR clearance.

11 DESCRIPTION

LIPITOR is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

LIPITOR Tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LIPITOR is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; LIPITOR also reduces LDL production and the number of LDL particles. LIPITOR reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

LIPITOR reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. LIPITOR also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. LIPITOR reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. LIPITOR reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

LIPITOR, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: LIPITOR is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to LIPITOR dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether LIPITOR is given with or without food. Plasma LIPITOR concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of LIPITOR is approximately 381 liters. LIPITOR is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, LIPITOR is likely to be secreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *Use in Specific Populations, Nursing Mothers (8.3)*].

Metabolism: LIPITOR is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of LIPITOR. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of LIPITOR metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of LIPITOR in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: LIPITOR and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of LIPITOR in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of LIPITOR is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of LIPITOR are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of LIPITOR in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with LIPITOR between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of LIPITOR; thus, dose adjustment in patients with renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5*), *Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of LIPITOR since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4.1)*].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	**Change in AUC[&]**	**Change in Cmax[&]**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑10.7 fold
[#]Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	↑ 5.9 fold	↑ 4.7 fold
[#]Ritonavir 400 mg BID/ saquinavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[#]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[#]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[#]Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[#]Rifampin 600 mg QD, 7 days (co-administered) [†]	40 mg SD	↑ 30%	↑ 2.7 fold
[#]Rifampin 600 mg QD, 5 days (doses separated) [†]	40 mg SD	↓ 80%	↓ 40%
[#]Gemfibrozil 600mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
[#]Fenofibrate 160mg QD, 7 days	40mg SD	↑ 3%	↑ 2%

[&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

[#] See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).

** Single sample taken 8-16 h post dose.

[†] Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	**Change in AUC**	**Change in Cmax**
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	[#] Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg - ethinyl estradiol 35μg	 ↑ 28% ↑ 19%	 ↑ 23% ↑ 30%

[#] See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

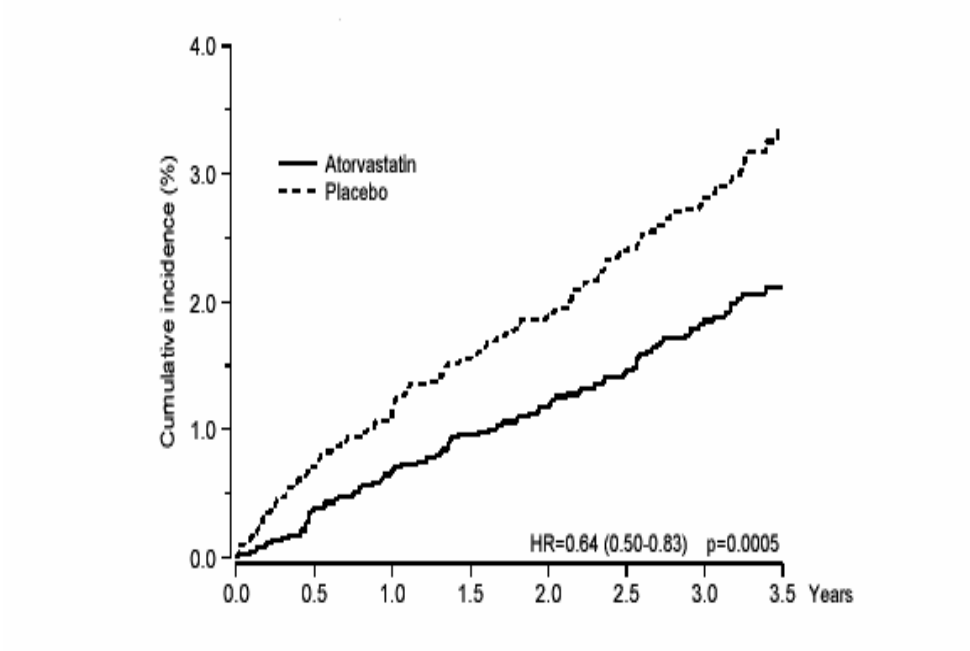
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40–80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients; <130/80 mm Hg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the LIPITOR group) or non-fatal MI (108 events in the placebo group vs. 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



LIPITOR also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of LIPITOR on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40–75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either LIPITOR 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

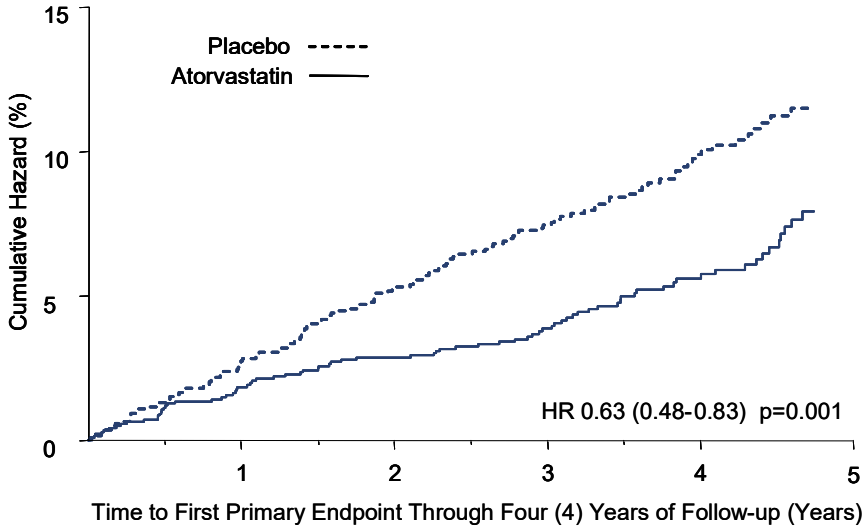
The effect of LIPITOR 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the LIPITOR group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of LIPITOR was seen regardless of age, sex, or baseline lipid levels.

LIPITOR significantly reduced the risk of stroke by 48% (21 events in the LIPITOR group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the LIPITOR group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the LIPITOR group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of LIPITOR 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In the Treating to New Targets Study (TNT), the effect of LIPITOR 80 mg/day vs. LIPITOR 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with LIPITOR 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of LIPITOR and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of LIPITOR and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of LIPITOR.

Treatment with LIPITOR 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Figure 3: Effect of LIPITOR 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

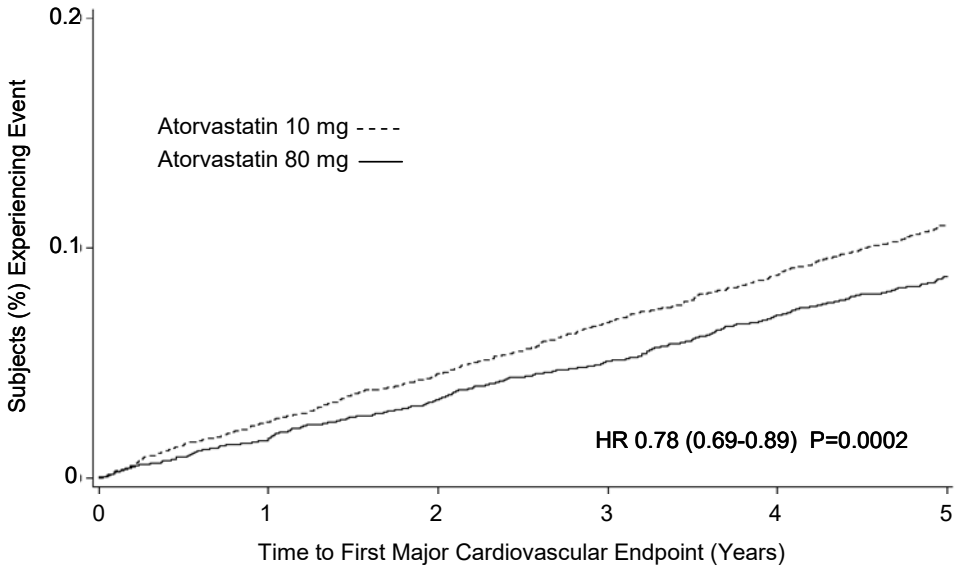


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg
b Component of other secondary endpoints
* Secondary endpoints not included in primary endpoint
HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft
Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with LIPITOR 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 5). Of the predefined secondary endpoints, treatment with LIPITOR 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 5). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with LIPITOR 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of LIPITOR and 105, 179, 142, 47, and 132 mg/dL during treatment with 20–40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the LIPITOR 80 mg/day group vs. 463 (10.4%) in the simvastatin 20–40 mg/day group, HR 0.89, 95% CI (0.78, 1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the LIPITOR 80 mg/day group vs. 374 (8.4%) in the simvastatin 20–40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the LIPITOR 80 mg group and the simvastatin 20–40 mg group.

14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

LIPITOR reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

LIPITOR is effective in a wide variety of patient populations with hyperlipidemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, LIPITOR given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 6.)

TABLE 6. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25^{th} and 75^{th} percentile) percent changes from baseline in HDL-C for LIPITOR 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hyperlipidemia, LIPITOR was compared to other statins. After randomization, patients were treated for 16 weeks with either LIPITOR 10 mg per day or a fixed dose of the comparative agent (Table 7).

TABLE 7. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
LIPITOR 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
LIPITOR 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
LIPITOR 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] A negative value for the 95% CI for the difference between treatments favors LIPITOR for all except HDL-C, for which a positive value favors LIPITOR. If the range does not include 0, this indicates a statistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$
[b] Significantly different from pravastatin, ANCOVA, $p \leq 0.05$
[c] Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 7 is not known. Table 7 does not contain data comparing the effects of LIPITOR 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

The response to LIPITOR in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 8). For the LIPITOR-treated patients, median (min, max) baseline TG level was 565 (267–1502).

TABLE 8. Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N=12)	LIPITOR 10 mg (N=37)	LIPITOR 20 mg (N=13)	LIPITOR 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

14.4 Dysbetalipoproteinemia *(Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below (Table 9).

TABLE 9. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	LIPITOR 10 mg	LIPITOR 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of LIPITOR. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to LIPITOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPITOR for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the LIPITOR group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of LIPITOR (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of LIPITOR-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

LIPITOR significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 10).

TABLE 10. Lipid-altering Effects of LIPITOR in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
LIPITOR	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the LIPITOR group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of LIPITOR therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

15 REFERENCES

[1] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, *Pediatrics.* 89(3):495-501. 1992.

16 HOW SUPPLIED/STORAGE AND HANDLING

10 mg tablets: coded “PD 155” on one side and “10” on the other.
NDC 0071-0155-23 bottles of 90
NDC 0071-0155-34 bottles of 5000
NDC 0071-0155-40 10 x 10 unit dose blisters

20 mg tablets: coded “PD 156” on one side and “20” on the other.
NDC 0071-0156-23 bottles of 90
NDC 0071-0156-40 10 x 10 unit dose blisters
NDC 0071-0156-94 bottles of 5000

40 mg tablets: coded “PD 157” on one side and “40” on the other.
NDC 0071-0157-23 bottles of 90
NDC 0071-0157-73 bottles of 500
NDC 0071-0157-88 bottles of 2500
NDC 0071-0157-40 10 x 10 unit dose blisters

80 mg tablets: coded “PD 158” on one side and “80” on the other.
NDC 0071-0158-23 bottles of 90
NDC 0071-0158-73 bottles of 500
NDC 0071-0158-88 bottles of 2500
NDC 0071-0158-92 8 x 8 unit dose blisters

Storage
Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients taking LIPITOR should be advised that cholesterol is a chronic condition and they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program as appropriate, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with atorvastatin *[*see *Warnings and Precautions (5.1)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking LIPITOR.

17.1 Muscle Pain
All patients starting therapy with LIPITOR should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes
It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

17.3 Pregnancy
Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using LIPITOR. Discuss future pregnancy plans with your patients, and discuss when to stop LIPITOR if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking LIPITOR and call their healthcare professional.

17.4 Breastfeeding
Women who are breastfeeding should be advised to not use LIPITOR. Patients who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

Rx Only

Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Distributed by:
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

LAB-0021-24.0
Revised June 2009

PATIENT INFORMATION

LIPITOR
atorvastatin calcium
tablets

(LIP-ih-tore))

Read the Patient Information that comes with LIPITOR before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

If you have any questions about LIPITOR, ask your doctor or pharmacist.

What is LIPITOR?

LIPITOR is a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. LIPITOR is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

LIPITOR can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

LIPITOR can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking, or high blood pressure.

LIPITOR starts to work in about 2 weeks.

What is Cholesterol?

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower your cholesterol if you have heart disease, smoke, have diabetes or high blood pressure, are older, or if heart disease starts early in your family.

Who Should Not Take LIPITOR?

Do not take LIPITOR if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Lipitor may harm your unborn baby. If you get pregnant, stop taking LIPITOR and call your doctor right away.
- are breast feeding**.** LIPITOR can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to LIPITOR or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in LIPITOR.

LIPITOR has not been studied in children under 10 years of age.

Before You Start LIPITOR

Tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with LIPITOR. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. LIPITOR and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How Should I Take LIPITOR?

- Take LIPITOR exactly as prescribed by your doctor. Do not change your dose or stop LIPITOR without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with LIPITOR. Your dose of LIPITOR may be changed based on these blood test results.
- Take LIPITOR each day at any time of day at about the same time each day. LIPITOR can be taken with or without food.

  Don't break LIPITOR tablets before taking.
- Your doctor should start you on a low-fat diet before giving you LIPITOR. Stay on this low-fat diet when you take LIPITOR.
- If you miss a dose of LIPITOR, take it as soon as you remember. Do not take LIPITOR if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of LIPITOR at the same time.
- If you take too much LIPITOR or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking LIPITOR?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. LIPITOR and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking LIPITOR right away and call your doctor.

What are the Possible Side Effects of LIPITOR?

LIPITOR can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or LIPITOR is stopped. These serious side effects include:

- **Muscle problems.** LIPITOR can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with LIPITOR.

- **Liver problems.** LIPITOR can cause liver problems. Your doctor may do blood tests to check your liver before you start taking LIPITOR, and while you take it.

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking LIPITOR: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with LIPITOR: tiredness, and tendon problems.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of LIPITOR. Ask your doctor or pharmacist for a complete list.

How do I store LIPITOR

- Store LIPITOR at room temperature, 68 to 77°F (20 to 25°C).
- Do not keep medicine that is out of date or that you no longer need.
- **Keep LIPITOR and all medicines out of the reach of children.** Be sure that if you throw medicine away, it is out of the reach of children.

General Information About LIPITOR

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use LIPITOR for a condition for which it was not prescribed. Do not give LIPITOR to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about LIPITOR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about LIPITOR that is written for health professionals. Or you can go to the LIPITOR website at www.lipitor.com.

What are the Ingredients in LIPITOR?

Active Ingredient: atorvastatin calcium
Inactive Ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

Rx Only

Distributed by:
Pfizer
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

Manufactured by Pfizer Ireland Pharmaceuticals
Dublin, Ireland

LAB-0348-4.0 June 2009

Footnote 7

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.

BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use
Initial U.S. Approval: 1989

WARNING: DISTANT SPREAD OF TOXIN EFFECT
See full prescribing information for complete boxed warning.
The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms. (5.2)

RECENT MAJOR CHANGES

- Warnings and Precautions (5.5, 5.7, 5.13, 5.14) 4/2017

INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) (1.2)
- Treatment of spasticity in adult patients (1.3)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.6)
- Treatment of strabismus in patients ≥12 years of age (1.6)

Important Limitations: Safety and effectiveness of BOTOX have not been established for:

- Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.2)
- Treatment of upper or lower limb spasticity in pediatric patients (1.3)
- Treatment of hyperhidrosis in body areas other than axillary (1.5)

DOSAGE AND ADMINISTRATION

- Follow indication-specific dosage and administration recommendations; Do not exceed a total dose of 400 Units administered in a 3 month interval (2.1)
- See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection (2.2)
- Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor (2.3)
- Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor (2.3)
- Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.4)
- Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.5)
- Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.5)
- Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients (2.6)
- Axillary Hyperhidrosis: 50 Units per axilla (2.7)
- Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.8)
- Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX (2.9)

DOSAGE FORMS AND STRENGTHS

Single-use, sterile 50 Units, 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection USP prior to injection (3)

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.4, 6)
- Infection at the proposed injection site (4.2)
- Intradetrusor Injections: Urinary Tract Infection or Urinary Retention (4.3)

WARNINGS AND PRECAUTIONS

- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.2, 5.6)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
- Bronchitis and upper respiratory tract infections in patients treated for spasticity (5.10)
- Urinary tract infections in patients treated for OAB (5.12)
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus. (5.13)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and >placebo) are (6.1):

- OAB: urinary tract infection, dysuria, urinary retention
- Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention
- Chronic Migraine: neck pain, headache
- Spasticity: pain in extremity
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Patients receiving concomitant treatment of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of BOTOX may be potentiated (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the prophylaxis of headaches in chronic migraine, treatment of OAB, detrusor overactivity associated with a neurologic condition, spasticity, and axillary hyperhidrosis; in patients under 16 years of age for treatment of cervical dystonia; and in patients under 12 years of age for treatment of blepharospasm and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses. ***[See Warnings and Precautions (5.2)]***

1 INDICATIONS AND USAGE

1.1 Bladder Dysfunction

Overactive Bladder

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Detrusor Overactivity associated with a Neurologic Condition

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

1.2 Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

Important Limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

1.3 Spasticity

Upper Limb Spasticity

BOTOX is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), finger flexors (flexor digitorum profundus and flexor digitorum sublimis), and thumb flexors (adductor pollicis and flexor pollicis longus).

Lower Limb Spasticity

BOTOX is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus).

Important Limitations

Safety and effectiveness of BOTOX have not been established for the treatment of other upper or lower limb muscle groups. Safety and effectiveness of BOTOX have not been established for the treatment of spasticity in pediatric patients under age 18 years. BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens.

1.4 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.5 Primary Axillary Hyperhidrosis

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Important Limitations

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively.

Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

1.6 Blepharospasm and Strabismus

BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe Use

The potency Units of BOTOX (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Warnings and Precautions (5.1) and Description (11)]*.

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3 month interval.

The safe and effective use of BOTOX depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. An understanding of standard electromyographic techniques is also required for treatment of strabismus, upper or lower limb spasticity, and may be useful for the treatment of cervical dystonia. Physicians administering BOTOX must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs.

2.2 Preparation and Dilution Technique

Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe (see Table 1, or for specific instructions for detrusor overactivity associated with a neurologic condition see Section 2.3), and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX should be stored in a refrigerator (2° to 8°C).

Table 1: Dilution Instructions for BOTOX Vials (50 Units, 100 Units and 200 Units)**

Diluent* Added to 50 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 200 Unit Vial	Resulting Dose Units per 0.1 mL
1 mL	5 Units	1 mL	10 Units	1 mL	20 Units
2 mL	2.5 Units	2 mL	5 Units	2 mL	10 Units
4 mL	1.25 Units	4 mL	2.5 Units	4 mL	5 Units
		8 mL	1.25 Units	8 mL	2.5 Units
		10 mL	1 Unit	10 mL	2 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

**For Detrusor Overactivity associated with a Neurologic Condition Dilution see Section 2.3

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

An injection of BOTOX is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile needle and syringe should be used to enter the vial on each occasion for removal of BOTOX.

Reconstituted BOTOX should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

2.3 Bladder Dysfunction

General

Patients must not have a urinary tract infection (UTI) at the time of treatment. Prophylactic antibiotics, except aminoglycosides, *[see Drug Interactions (7.1)]* should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of procedure-related UTI.

Patients should discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder

An intravesical instillation of diluted local anesthetic with or without sedation may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 100 Units of BOTOX, and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Dispose of any unused saline.

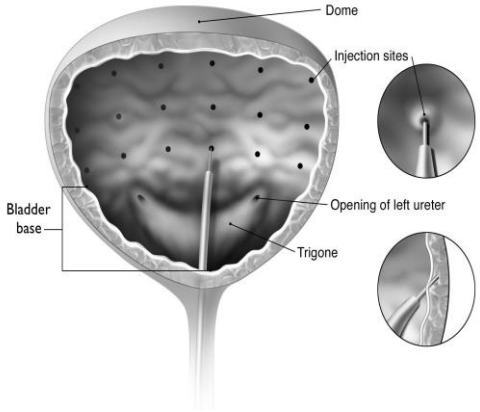
Reconstituted BOTOX (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, patients should demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median time until patients qualified for the second treatment of BOTOX in double-blind, placebo-controlled clinical studies was 169 days [~24 weeks]), but no sooner than 12 weeks from the prior bladder injection.

Figure 1: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Detrusor Overactivity associated with a Neurologic Condition



Detrusor Overactivity associated with a Neurologic Condition

An intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 Units of BOTOX per treatment, and should not be exceeded.

200 Unit Vial of BOTOX

- Reconstitute a 200 Unit vial of BOTOX with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
- Draw 2 mL from the vial into each of three 10 mL syringes.
- Complete the reconstitution by adding 8 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

100 Unit Vial of BOTOX

- Reconstitute two 100 Unit vials of BOTOX, each with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vials gently.
- Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe for a total of 4 mL in each syringe.
- Complete the reconstitution by adding 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstituted BOTOX (200 Units/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, placebo-controlled clinical studies was 295-337 days [42-48 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

2.4 Chronic Migraine

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL (see Table 1). The recommended dose for treating chronic migraine is 155 Units administered intramuscularly using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams and Table 2 below. A one inch needle may be needed in the neck region for patients with thick neck muscles. With the exception of the procerus muscle, which should be injected at one site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck. The recommended re-treatment schedule is every 12 weeks.

Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine

1 2 3 4

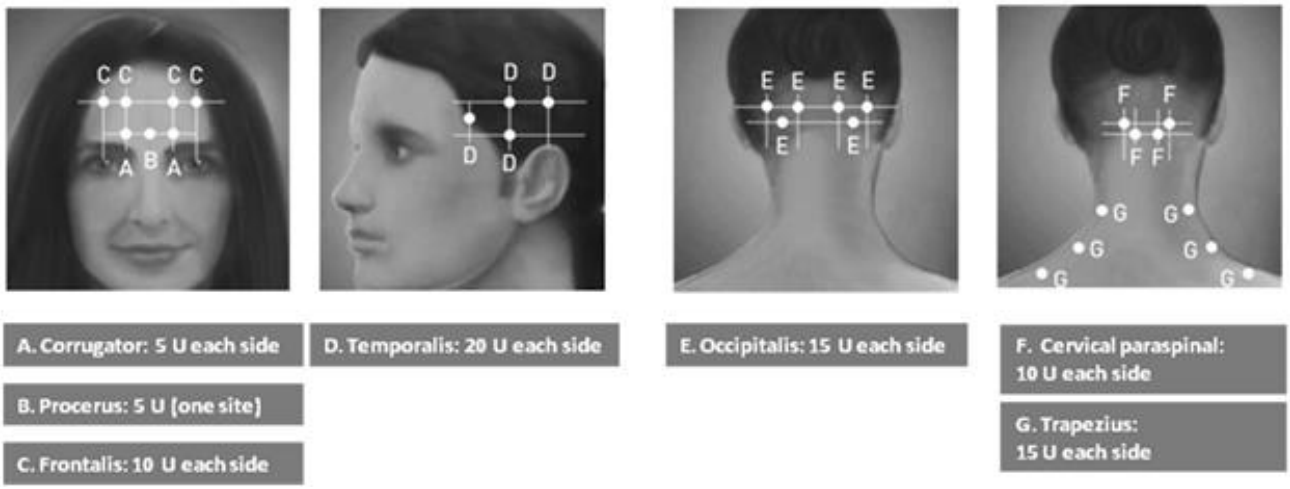


Table 2: BOTOX Dosing by Muscle for Chronic Migraine

Head/Neck Area	Recommended Dose (Number of Sites[a])
Frontalis[b]	20 Units divided in 4 sites
Corrugator[b]	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis[b]	30 Units divided in 6 sites
Temporalis[b]	40 Units divided in 8 sites
Trapezius[b]	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group[b]	20 Units divided in 4 sites
Total Dose:	**155 Units** divided **in 31 sites**

[a] Each IM injection site = 0.1 mL = 5 Units BOTOX
[b] Dose distributed bilaterally

2.5 Spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, or adverse event history with BOTOX.

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with techniques such as needle electromyographic guidance or nerve stimulation is recommended.

Repeat BOTOX treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected.

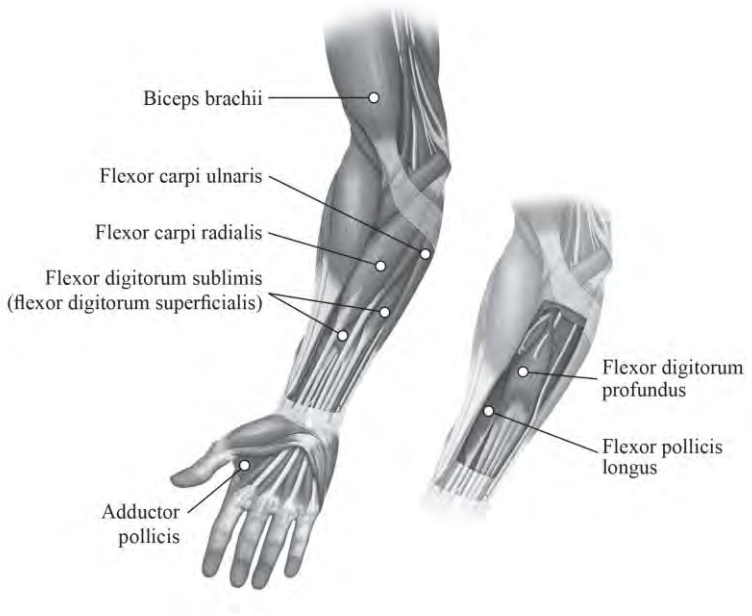
Upper Limb Spasticity

In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 3 and Figure 2) at a given treatment session.

Table 3: BOTOX Dosing by Muscle for Upper Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Biceps Brachii	100 Units-200 Units divided in 4 sites
Flexor Carpi Radialis	12.5 Units-50 Units in 1 site
Flexor Carpi Ulnaris	12.5 Units-50 Units in 1 site
Flexor Digitorum Profundus	30 Units-50 Units in 1 site
Flexor Digitorum Sublimis	30 Units-50 Units in 1 site
Adductor Pollicis	20 Units in 1 site
Flexor Pollicis Longus	20 Units in 1 site

Figure 2: Injection Sites for Upper Limb Spasticity



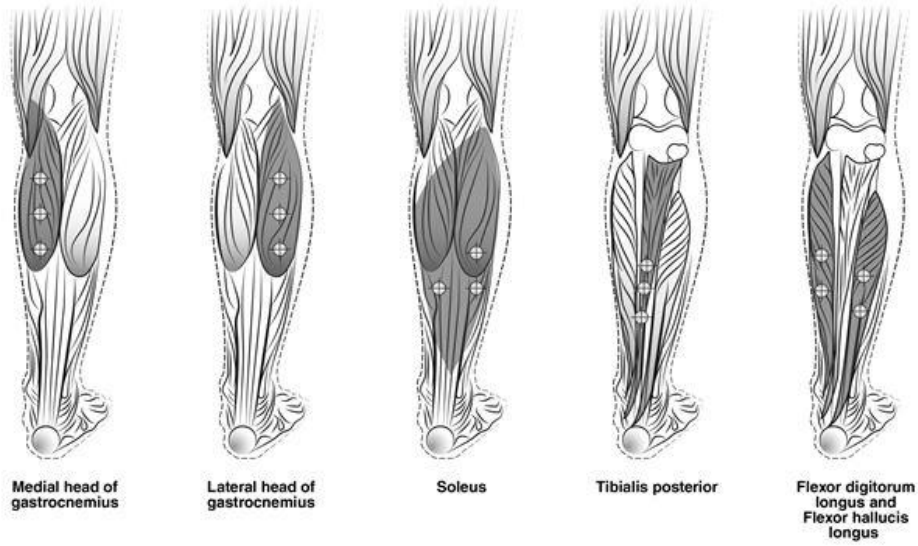
Lower Limb Spasticity

The recommended dose for treating lower limb spasticity is 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus) (see Table 4 and Figure 3).

Table 4: BOTOX Dosing by Muscle for Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	75 Units divided in 3 sites
Gastrocnemius lateral head	75 Units divided in 3 sites
Soleus	75 Units divided in 3 sites
Tibialis Posterior	75 Units divided in 3 sites
Flexor hallucis longus	50 Units divided in 2 sites
Flexor digitorum longus	50 Units divided in 2 sites

Figure 3: Injection Sites for Lower Limb Spasticity



2.6 Cervical Dystonia

A double-blind, placebo-controlled study enrolled patients who had extended histories of receiving and tolerating BOTOX injections, with prior individualized adjustment of dose. The mean BOTOX dose administered to patients in this study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The BOTOX dose was divided among the affected muscles *[see Clinical Studies (14.5)]*.

Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of BOTOX should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscle to 100 Units or less may decrease the occurrence of dysphagia *[see Warnings and Precautions (5.2, 5.5, 5.6)]*.

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 1). In general, no more than 50 Units per site should be administered using a sterile needle (e.g., 25-30 gauge) of an appropriate length. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the double-blind, placebo-controlled study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

2.7 Primary Axillary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Table 1). Using a sterile 30 gauge needle, 50 Units of BOTOX (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

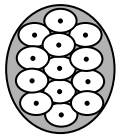
Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine-Starch Test Procedure:

Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 4.

Figure 4: Injection Pattern for Primary Axillary Hyperhidrosis



Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface, with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject BOTOX directly through the ink mark to avoid a permanent tattoo effect.

2.8 Blepharospasm

For blepharospasm, reconstituted BOTOX is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units-2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Table 1).

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient, usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. Some tolerance may be found when BOTOX is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of BOTOX treatment for blepharospasm in a 30-day period should not exceed 200 Units.

2.9 Strabismus

BOTOX is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for BOTOX injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

The volume of BOTOX injected for treatment of strabismus should be between 0.05-0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX *[see Dosage and Administration (2.2)]* typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

Initial Doses in Units

Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

- For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
- For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

Subsequent Doses for Residual or Recurrent Strabismus

- It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
- Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
- Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
- Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
- The maximum recommended dose as a single injection for any one muscle is 25 Units.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Table 1).

3 DOSAGE FORMS AND STRENGTHS

Single-use, sterile 50 Units, 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection USP prior to injection.

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions (5.4)]*.

4.2 Infection at the Injection Site(s)

BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

4.3 Urinary Tract Infection or Urinary Retention

Intradetrusor injection of BOTOX is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection. Intradetrusor injection of BOTOX is also contraindicated in patients with urinary retention and in patients with post-void residual (PVR) urine volume >200 mL, who are not routinely performing clean intermittent self-catheterization (CIC).

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description (11)]*.

5.2 Spread of Toxin Effect

Postmarketing safety data from BOTOX and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for blepharospasm at the recommended dose (30 Units and below), severe primary axillary hyperhidrosis at the recommended dose (100 Units), strabismus, or for chronic migraine at the labeled doses have been reported.

5.3 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

5.4 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

5.5 Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects

including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX *[see Warnings and Precautions (5.2, 5.6)]*.

5.6 Dysphagia and Breathing Difficulties

Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing *[see Warnings and Precautions (5.2)]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions (5.2)]*.

5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV_1 40-80% of predicted value and $FEV_1/FVC \leq 0.75$), the event rate in change of Forced Vital Capacity (FVC) ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 5).

Table 5: Event Rate Per Patient Treatment Cycle Among Patients with Reduced Lung Function Who Experienced at Least a 15% or 20% Decrease in FVC From Baseline at Week 1, 6, 12 Post-injection with Up to Two Treatment Cycles with BOTOX or Placebo

	BOTOX 360 Units		**BOTOX 240 Units**		**Placebo**	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo *[see Warnings and Precautions (5.10)]*.

In a double-blind, placebo-controlled, parallel group study in adult patients with detrusor overactivity associated with a neurologic condition and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 6).

Table 6: Number and Percent of Patients Experiencing at Least a 15% or 20% Decrease in FVC From Baseline at Week 2, 6, 12 Post-injection with BOTOX or Placebo

	BOTOX 200 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%
Week 2	0/15 (0%)	0/15 (0%)	1/11 (9%)	0/11 (0%)
Week 6	2/13 (15%)	1/13 (8%)	0/12 (0%)	0/12 (0%)
Week 12	0/12(0%)	0/12 (0%)	0/7 (0%)	0/7 (0%)

5.8 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

Reduced blinking from BOTOX injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of BOTOX for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

5.11 Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition

Autonomic dysreflexia associated with intradetrusor injections of BOTOX could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. In clinical trials, the incidence of autonomic dysreflexia was greater in patients treated with BOTOX 200 Units compared with placebo (1.5% versus 0.4%, respectively).

5.12 Urinary Tract Infections in Patients with Overactive Bladder

BOTOX increases the incidence of urinary tract infection *[see Adverse Reactions (6.1)]*. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

5.13 Urinary Retention in Patients Treated for Bladder Dysfunction

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

The incidence and duration of urinary retention is described below for patients with overactive bladder and detrusor overactivity associated with a neurologic condition who received BOTOX or placebo injections.

Overactive Bladder

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterization (CIC) for urinary retention following treatment with BOTOX or placebo is shown in Table 7. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 7: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB

Timepoint	BOTOX 100 Units (N=552)	Placebo (N=542)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	6.5% (n=36)	0.4% (n=2)
Duration of Catheterization for Urinary Retention (Days)		
Median	63	11
Min, Max	1, 214	3, 18

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 8.

Table 8. Proportion of Patients Experiencing Urinary Retention Following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB According to History of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

Detrusor Overactivity associated with a Neurologic Condition

In two double-blind, placebo-controlled trials in patients with detrusor overactivity associated with a neurologic condition (NDO-1 and NDO-2), the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX 200 Units or placebo is shown in Table 9. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 9: Proportion of Patients Not Using CIC at Baseline and then Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-blind, Placebo-controlled Clinical Trials

Timepoint	BOTOX 200 Units (N=108)	Placebo (N=104)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	30.6% (n=33)	6.7% (n=7)
Duration of Catheterization for Urinary Retention (Days)		
Median	289	358
Min, Max	1, 530	2, 379

Among patients not using CIC at baseline, those with Multiple Sclerosis (MS) were more likely to require CIC post-injection than those with Spinal Cord Injury (SCI) (see Table 10).

Table 10: Proportion of Patients by Etiology (MS and SCI) Not Using CIC at Baseline and then Catheterizing for Urinary Retention Following an Injection in Double-blind, Placebo-controlled Clinical Trials

Timepoint/	MS		SCI	
	BOTOX 200 Units (N=86)	Placebo (N=88)	BOTOX 200 Units (N=22)	Placebo (N=16)
At any time during complete treatment cycle	31% (n=27)	5% (n=4)	27% (n=6)	19% (n=3)

A placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) was conducted in non-catheterizing MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. Catheterization for urinary retention was initiated in 15.2% (10/66) of patients following treatment with BOTOX 100 Units versus 2.6% (2/78) on placebo at any time during the complete treatment cycle. The median duration of post-injection catheterization for those who developed urinary retention was 64 days for BOTOX 100 Units and 2 days for placebo.

5.14 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

6 ADVERSE REACTIONS

The following adverse reactions to BOTOX (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.2)]*
- Serious Adverse Reactions with Unapproved Use *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Contraindications (4.1) and Warnings and Precautions (5.4)]*
- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders *[see Warnings and Precautions (5.5)]*
- Dysphagia and Breathing Difficulties *[see Warnings and Precautions (5.6)]*
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition *[see Warnings and Precautions (5.7)]*
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm *[see Warnings and Precautions (5.8)]*
- Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus *[see Warnings and Precautions (5.9)]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions (5.10)]*
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition *[see Warnings and Precautions (5.11)]*
- Urinary Tract Infections in Patients with Overactive Bladder *[see Warnings and Precautions (5.12)]*
- Urinary Retention in Patients Treated for Bladder Dysfunction *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse reactions observed with the use of BOTOX Cosmetic also have the potential to be observed with the use of BOTOX.

In general, adverse reactions occur within the first week following injection of BOTOX and, while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment. Needle-related pain and/or anxiety may result in vasovagal responses (including syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions (5.2)]*.

Overactive Bladder

Table 11 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 11: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Often than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection, in Double-blind, Placebo-controlled Clinical Trials in Patients with OAB

Adverse Reactions	BOTOX 100 Units (N=552)	Placebo (N=542)
Urinary tract infection	99 (18%)	30 (6%)
Dysuria	50 (9%)	36 (7%)
Urinary retention	31 (6%)	2 (0%)
Bacteriuria	24 (4%)	11 (2%)
Residual urine volume*	17 (3%)	1 (0%)

*Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥350 mL regardless of symptoms, and for PVR ≥200 mL to <350 mL with symptoms (e.g., voiding difficulty).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 12.

Table 12: Proportion of Patients Experiencing Urinary Tract Infection following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB according to history of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary tract infection (UTI)	25 (31%)	8 (12%)	135 (26%)	51 (10%)

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

Detrusor Overactivity associated with a Neurologic Condition
Table 13 presents the most frequently reported adverse reactions in the two Phase 3 double-blind, placebo-controlled studies (NDO-1 and NDO-2) within 12 weeks of injection for patients with detrusor overactivity associated with a neurologic condition treated with BOTOX 200 Units.

Table 13: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection in Double-blind, Placebo-controlled Clinical Trials (NDO-1 and NDO-2)

Adverse Reactions	BOTOX 200 Units (N=262)	Placebo (N=272)
Urinary tract infection	64 (24%)	47 (17%)
Urinary retention	45 (17%)	8 (3%)
Hematuria	10 (4%)	8 (3%)

The following adverse reactions with BOTOX 200 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 44 weeks): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

In the Multiple Sclerosis (MS) patients enrolled in the double-blind, placebo-controlled trials, the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX and 0.20 for placebo.

No change was observed in the overall safety profile with repeat dosing.

Table 14 presents the most frequently reported adverse reactions in a placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) conducted in MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least one anticholinergic agent and not catheterized at baseline. The table below presents the most frequently reported adverse reactions within 12 weeks of injection.

Table 14: Adverse Reactions Reported by >2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection (NDO-3)

Adverse Reactions	BOTOX 100 Unit (N=66)	Placebo (N=78)
Urinary tract infection	17 (26%)	5 (6%)
Bacteriuria	6 (9%)	4 (5%)
Urinary retention	10 (15%)	1 (1%)
Dysuria	3 (5%)	1 (1%)
Residual urine volume*	11 (17%)	1 (1%)

* Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥350 mL regardless of symptoms, and for PVR ≥200 mL to <350 mL with symptoms (e.g., voiding difficulty).

The following adverse events with BOTOX 100 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 51 weeks): urinary tract infections (39%), bacteriuria (18%), urinary retention (17%), residual urine volume* (17%), dysuria (9%), and hematuria (5%).

No difference in the MS exacerbation annualized rate (i.e., number of MS exacerbating events per patient-year) was observed (BOTOX =0, placebo =0.07).

Chronic Migraine
In double-blind, placebo-controlled chronic migraine efficacy trials (Study 1 and Study 2), the discontinuation rate was 12% in the BOTOX treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the BOTOX group and 1% in the placebo group. The most frequent adverse events leading to discontinuation in the BOTOX group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis.

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 15.

Table 15: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by System Organ Class	BOTOX 155 Units-195 Units (N=687)	Placebo (N=692)
Nervous system disorders		
Headache	32 (5%)	22 (3%)
Migraine	26 (4%)	18 (3%)
Facial paresis	15 (2%)	0 (0%)
Eye disorders		
Eyelid ptosis	25 (4%)	2 (<1%)
Infections and Infestations		
Bronchitis	17 (3%)	11 (2%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (9%)	19 (3%)
Musculoskeletal stiffness	25 (4%)	6 (1%)
Muscular weakness	24 (4%)	2 (<1%)
Myalgia	21 (3%)	6 (1%)
Musculoskeletal pain	18 (3%)	10 (1%)
Muscle spasms	13 (2%)	6 (1%)
General disorders and administration site conditions		
Injection site pain	23 (3%)	14 (2%)
Vascular Disorders		
Hypertension	11 (2%)	7 (1%)

Other adverse reactions that occurred more frequently in the BOTOX group compared to the placebo group at a frequency less than 1% and potentially BOTOX related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Upper Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX for adult upper limb spasticity appear in Table 16.

Table 16: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by System Organ Class	BOTOX 251 Units-360 Units (N=115)	BOTOX 150 Units-250 Units (N=188)	BOTOX <150 Units (N=54)	Placebo (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions				
Fatigue	4 (3%)	4 (2%)	1 (2%)	0
Infections and infestations				
Bronchitis	4 (3%)	4 (2%)	0	2 (1%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	7 (6%)	10 (5%)	5 (9%)	8 (4%)
Muscular weakness	0	7 (4%)	1 (2%)	2 (1%)

Twenty two adult patients, enrolled in double-blind placebo controlled studies, received 400 Units or higher of BOTOX for treatment of upper limb spasticity. In addition, 44 adults received 400 Units of BOTOX or higher for four consecutive treatments over approximately one year for treatment of upper limb spasticity. The type and frequency of adverse reactions observed in patients treated with 400 Units of BOTOX were similar to those reported in patients treated for upper limb spasticity with 360 Units of BOTOX.

Lower Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 17. Two hundred thirty one patients enrolled in a double-blind placebo controlled study (Study 6) received 300 Units to 400 Units of BOTOX, and were compared with 233 patients who received placebo. Patients were followed for an average of 91 days after injection.

Table 17: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 6)

Adverse Reactions	BOTOX (N=231)	Placebo (N=233)
Musculoskeletal and connective tissue disorders		
Arthralgia	8 (3%)	2 (1%)
Back pain	6 (3%)	4 (2%)
Myalgia	4 (2%)	3 (1%)
Infections and infestations		
Upper respiratory tract infection	4 (2%)	2 (1%)
General disorders and administration site conditions		
Injection site pain	5 (2%)	2 (1%)

Cervical Dystonia
In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles *[see Warnings and Precautions (5.2, 5.6)]*.

The most common severe adverse reaction associated with the use of BOTOX injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea *[see Warnings and Precautions (5.2, 5.6)]*. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms *[see Warnings and Precautions (5.6)]*.

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of BOTOX for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis
The most frequently reported adverse reactions (3-10% of adult patients) following injection of BOTOX in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to BOTOX 50 Units and 110 patients exposed to BOTOX 75 Units in each axilla.

Blepharospasm
In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured BOTOX, the most frequently reported adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder, reduced blinking from BOTOX injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus
Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of BOTOX. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%. The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to onabotulinumtoxinA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of BOTOX, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to BOTOX therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to BOTOX therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%) and no patients among 406 migraine patients with analyzed specimens developed the presence of neutralizing antibodies.

In overactive bladder patients with analyzed specimens from the two phase 3 studies and the open-label extension study, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. Response to subsequent BOTOX treatment was not different following seroconversion in these three patients.

In detrusor overactivity associated with neurologic condition patients with analyzed specimens in the drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Following development of neutralizing

antibodies in these 8 patients, 4 continued to experience clinical benefit, 2 did not experience clinical benefit, and the effect on the response to BOTOX in the remaining 2 patients is not known.

The data reflect the patients whose test results were considered positive for neutralizing activity to BOTOX in a mouse protection assay or negative based on a screening ELISA assay or mouse protection assay.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy; denervation/muscle atrophy; diarrhea; hyperhidrosis; hypoacusis; hypoaesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions (5.4, 5.6)]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

7 DRUG INTERACTIONS

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

Co-administration of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

7.2 Anticholinergic Drugs

Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects.

7.3 Other Botulinum Neurotoxin Products

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

7.4 Muscle Relaxants

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX in pregnant women. In animal studies, administration of BOTOX during pregnancy resulted in adverse effects on fetal growth (decreased fetal weight and skeletal ossification) at clinically relevant doses, which were associated with maternal toxicity *[see Data)]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated populations is unknown.

Data

Animal Data

When BOTOX (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately equal to the human dose of 400 Units, on a body weight basis (Units/kg).

When BOTOX was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the human dose of 400 Units, based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 2 times the human dose of 400 Units, based on Units/kg.

8.2 Lactation

Risk Summary

There are no data on the presence of BOTOX in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BOTOX and any potential adverse effects on the breastfed infant from BOTOX or from the underlying maternal conditions.

8.4 Pediatric Use

Bladder Dysfunction

Safety and effectiveness in patients below the age of 18 years have not been established.

Prophylaxis of Headaches in Chronic Migraine

Safety and effectiveness in patients below the age of 18 years have not been established.

Spasticity

Safety and effectiveness in patients below the age of 18 years have not been established.

Axillary Hyperhidrosis

Safety and effectiveness in patients below the age of 18 years have not been established.

Cervical Dystonia

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Blepharospasm and Strabismus

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

8.5 Geriatric Use

Of the 2145 patients in placebo-controlled clinical studies of BOTOX for the treatment of spasticity, 33.5% were 65 or older, and 7.7% were 75 years of age or older. No overall differences in safety were observed between elderly patients and younger patients.

In clinical studies of BOTOX across other indications, no overall differences in safety were observed between elderly patients and younger patients, with the exception of Overactive Bladder (see below). Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Overactive Bladder

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% were 65 years of age or older, and 14.7% were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 18). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

Table 18: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

	<65 Years		65 to 74 Years		≥75 Years	
Adverse Reactions	**BOTOX 100 Units (N=344)**	**Placebo (N=348)**	**BOTOX 100 Units (N=169)**	**Placebo (N=151)**	**BOTOX 100 Units (N=94)**	**Placebo (N=86)**
Urinary tract infection	73 (21%)	23 (7%)	51 (30%)	20 (13%)	36 (38%)	16 (19%)
Urinary retention	21 (6%)	2 (0.6%)	14 (8%)	0 (0%)	8 (9%)	1 (1%)

Observed effectiveness was comparable between these age groups in placebo-controlled clinical studies.

10 OVERDOSAGE

Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection *[see Boxed Warning and Warnings and Precautions (5.2, 5.6)]*. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

11 DESCRIPTION

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A, and intended for intramuscular, intradetrusor and intradermal use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

The primary release procedure for BOTOX uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products BOTOX and BOTOX Cosmetic. One Unit of BOTOX corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of BOTOX contains either 50 Units of Clostridium botulinum type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride; 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride; or 200 Units of Clostridium botulinum type A neurotoxin complex, 1 mg of Albumin Human, and 1.8 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or autonomic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX.

When injected intradermally, BOTOX produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

12.3 Pharmacokinetics

Using currently available analytical technology, it is not possible to detect BOTOX in the peripheral blood following intramuscular injection at the recommended doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX.

Mutagenesis

BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicology assays.

Impairment of Fertility

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males: 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the human dose of 400 Units, on a body weight basis (Units/kg).

13.2 Animal Toxicology and/or Pharmacology

In a study to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 Units/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 Units/kg (~12X the highest human bladder dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injections up to 100 Units/kg (~33X the highest human bladder dose [200 Units], based on Units/kg).

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

Two double-blind, placebo-controlled, randomized, multi-center, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency (Studies OAB-1 and OAB-2). Patients needed to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days to enter the studies. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 Units of BOTOX (n=557), or placebo (n=548). Patients received 20 injections of study drug (5 units of BOTOX or placebo) spaced approximately 1 cm apart into the detrusor muscle.

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 19 and 20, and Figures 5 and 6.

Table 19: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

	BOTOX 100 Units (N=278)	Placebo (N=272)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean Baseline	5.5	5.1		
Mean Change[*] at Week 2	-2.6	-1.0	-1.6	
Mean Change[*] at Week 6	-2.8	-1.0	-1.8	
Mean Change[*] at Week 12[**]	-2.5	-0.9	-1.6 (-2.1, -1.2)	<0.001
Daily Frequency of Micturition Episodes[b]				
Mean Baseline	12.0	11.2		
Mean Change[†] at Week 12[**]	-1.9	-0.9	-1.0 (-1.5, -0.6)	<0.001
Volume Voided per Micturition[b] (mL)				
Mean Baseline	156	161		
Mean Change[†] at Week 12[**]	38	8	30 (17, 43)	<0.001

[*] Least squares (LS) mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. Last observation carried forward (LOCF) values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

[**] Primary timepoint

[a] Primary variable

[b] Secondary variable

Table 20: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

	BOTOX 100 Units (N=275)	Placebo (N=269)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean Baseline	5.5	5.7		
Mean Change[*] at Week 2	-2.7	-1.1	-1.6	
Mean Change[*] at Week 6	-3.1	-1.3	-1.8	
Mean Change[*] at Week 12[**]	-3.0	-1.1	-1.9 (-2.5, -1.4)	<0.001
Daily Frequency of Micturition Episodes[b]				
Mean Baseline	12.0	11.8		
Mean Change[†] at Week 12[**]	-2.3	-0.6	-1.7 (-2.2, -1.3)	<0.001
Volume Voided per Micturition[b] (mL)				
Mean Baseline	144	153		
Mean Change[†] at Week 12[**]	40	10	31 (20, 41)	<0.001

[*] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

[**] Primary timepoint

[a] Primary variable

[b] Secondary variable

Figure 5: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-1

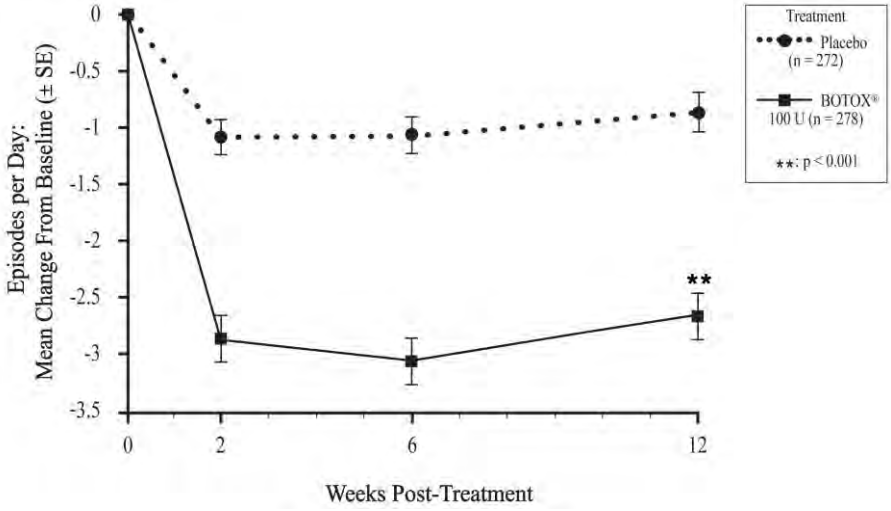
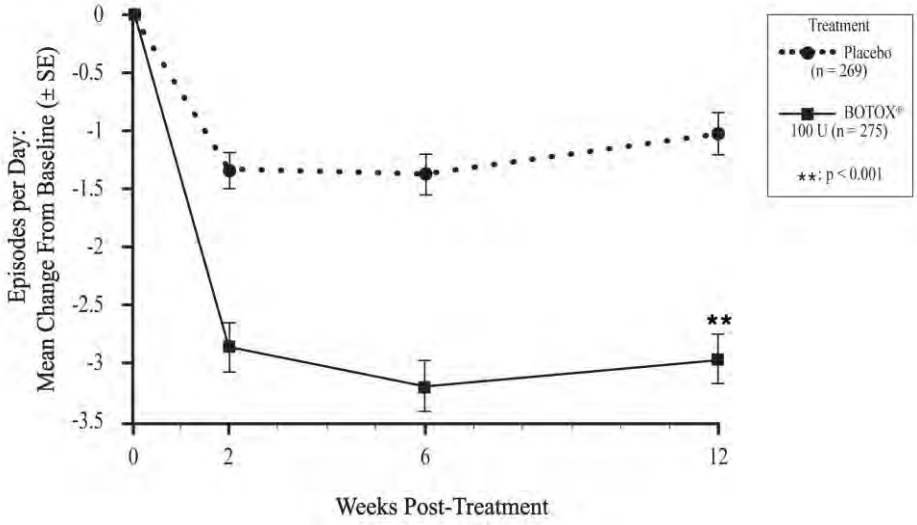


Figure 6: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-2



The median duration of response in Study OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19-24 weeks for the BOTOX 100 Unit dose group compared to 13 weeks for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days.

14.2 Detrusor Overactivity associated with a Neurologic Condition

Two double-blind, placebo-controlled, randomized, multi-center clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (Studies NDO-1 and NDO-2). A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 21 and 22, and Figures 7 and 8.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.

Table 21: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) Study NDO-1

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	134	146		
Mean Baseline	32.3	28.3		
Mean Change* at Week 2	-15.3	-10.0	-5.3	—
Mean Change* at Week 6**	-19.9	-10.6	-9.2 (-13.1, -5.3)	p<0.001
Mean Change* at Week 12	-19.8	-8.8	-11.0	—
Maximum Cystometric Capacity[b] **(mL)**				
N	123	129		
Mean Baseline	253.8	259.1		
Mean Change* at Week 6**	135.9	12.1	123.9 (89.1, 158.7)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] **(cmH_2O)**				
N	41	103		
Mean Baseline	63.1	57.4		
Mean Change* at Week 6**	-28.1	-3.7	-24.4	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

Table 22: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) in Study NDO-2

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	91	91		
Mean Baseline	32.7	36.8		
Mean Change* at Week 2	-18.0	-7.9	-10.1	—
Mean Change* at Week 6**	-19.6	-10.8	-8.8 (-14.5, -3.0)	p=0.003
Mean Change* at Week 12	-19.6	-10.7	-8.9	—
Maximum Cystometric Capacity[b] **(mL)**				
N	88	85		
Mean Baseline	239.6	253.8		
Mean Change* at Week 6**	150.8	2.8	148.0 (101.8, 194.2)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] **(cmH_2O)**				
N	29	68		
Mean Baseline	65.6	43.7		
Mean Change* at Week 6**	-28.7	2.1	-30.7	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

Figure 7: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-1

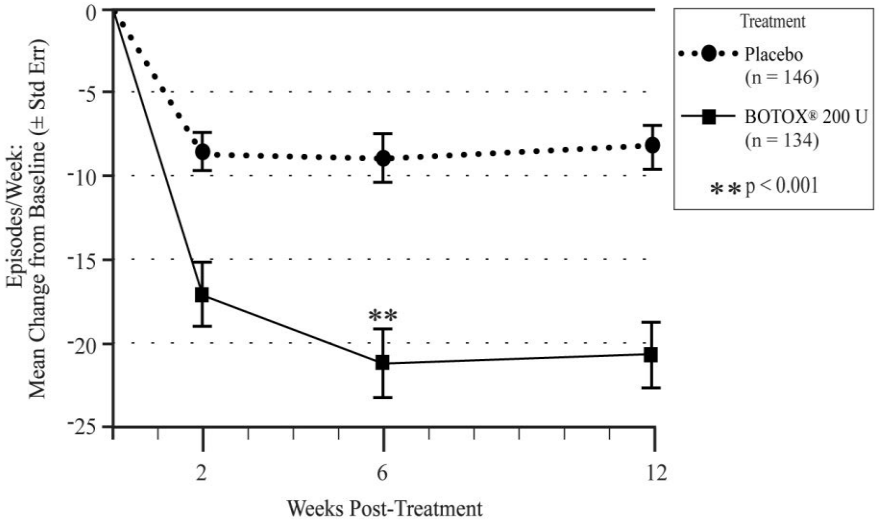
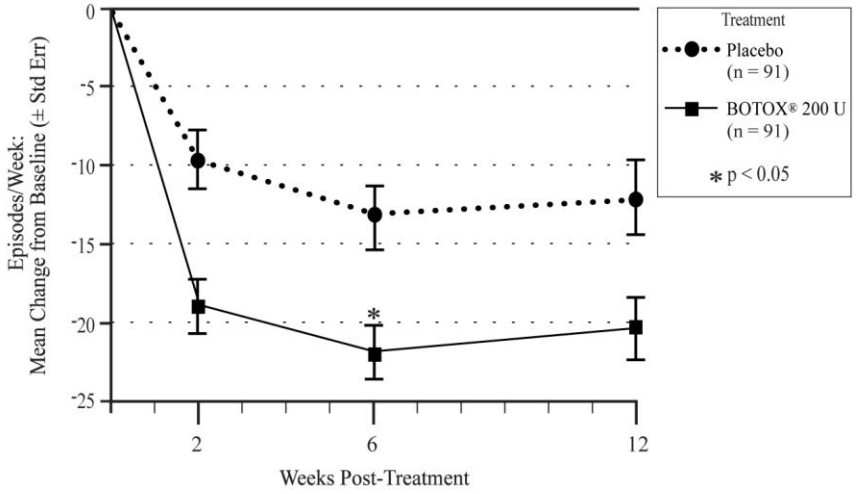


Figure 8: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-2



The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295-337 days (42-48 weeks) for the 200 Units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2).

A placebo-controlled, double-blind randomized post-approval 52 week study (Study NDO-3) was conducted in MS patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. These patients were randomized to receive either 100 Units of BOTOX (n=66) or placebo (n=78).

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for BOTOX® (100 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Table 23.

Table 23: Baseline and Change from Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) in Study NDO-3

	BOTOX 100 Units	Placebo	Treatment Difference*	p-value*
Daily Frequency of Urinary Incontinence Episodes[a]				
N	66	78		
Mean Baseline	4.2	4.3		
Mean Change* at Week 2	-2.9	-1.2	-1.7	—
Mean Change* at Week 6**	-3.4	-1.1	-2.3 (-3.0, -1.7)	p<0.001
Mean Change* at Week 12	-2.7	-1.0	-1.8	—
Maximum Cystometric Capacity[b] (mL)				
N	62	72		
Mean Baseline	248.9	245.5		
Mean Change* at Week 6**	134.4	3.5	130.9 (94.8, 167.0)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	25	51		
Mean Baseline	42.4	39.0		
Mean Change* at Week 6**	-19.2	2.7	-21.9 (-37.5, -6.3)	

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline daily endpoint as covariate and treatment group and propensity score stratification as factors. LOCF values were used to analyze the primary efficacy variable.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

The median duration of response in study NDO-3, based on patient qualification for re-treatment was 362 days (52 weeks) for the BOTOX 100 Units dose group compared to 88 days (13 weeks) for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days with no more than 1 incontinence-free day.

14.3 Chronic Migraine

BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had ≥15 headache days lasting 4 hours or more, with ≥50% being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units BOTOX injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. BOTOX treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 24).

Table 24: Week 24 Key Efficacy Variables for Study 1 and Study 2

Efficacy per 28 days	Study 1		Study 2	
	BOTOX (N=341)	Placebo (N=338)	BOTOX (N=347)	Placebo (N=358)
Change from baseline in frequency of headache days	-7.8*	-6.4	-9.2*	-6.9
Change from baseline in total cumulative hours of headache on headache days	-107*	-70	-134*	-95

* Significantly different from placebo (p≤0.05)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.

Figure 9: Mean Change from Baseline in Number of Headache Days for Study 1

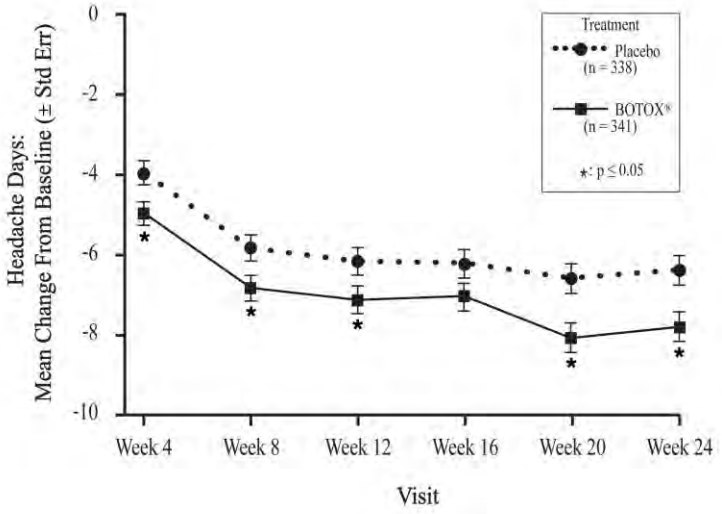
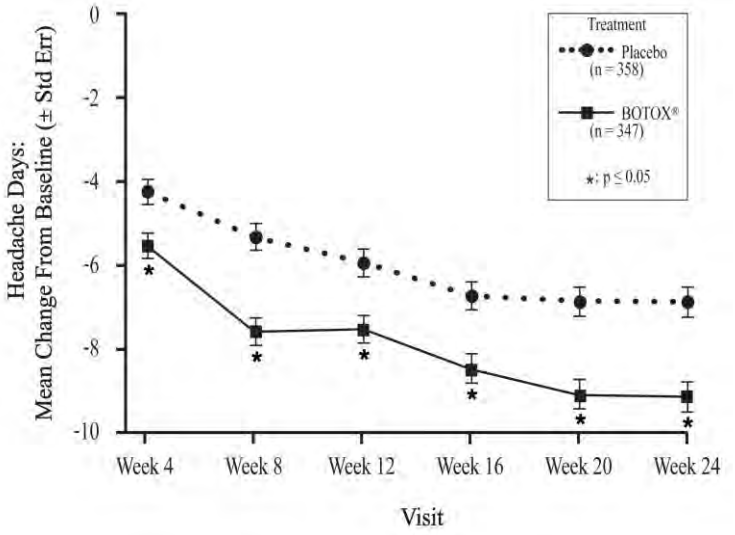


Figure 10: Mean Change from Baseline in Number of Headache Days for Study 2



14.4 Spasticity

Upper Limb Spasticity

The efficacy of BOTOX for the treatment of upper limb spasticity was evaluated in three randomized, multi-center, double-blind, placebo-controlled studies (Studies 1, 2, and 3). Two additional randomized, multi-center, double-blind, placebo-controlled studies for upper limb spasticity in adults also included the evaluation of the efficacy of BOTOX for the treatment of thumb spasticity (Studies 4 and 5).

Study 1 included 126 patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 25). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 25: Study Medication Dose and Injection Sites in Study 1

Muscles Injected	Volume (mL)	BOTOX (Units)	Number of Injection Sites
Wrist Flexor Carpi Radialis	1	50	1
Flexor Carpi Ulnaris	1	50	1
Finger Flexor Digitorum Profundus	1	50	1
Flexor Digitorum Sublimis	1	50	1
Thumb Adductor Pollicis[a]	0.4	20	1
Flexor Pollicis Longus[a]	0.4	20	1

[a] injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 5-point scale with grades of 0 [no increase in muscle tone] to 4 [limb rigid in flexion or extension]. It is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 26.

Table 26: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

	BOTOX (N=64)	Placebo (N=62)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†[a]	-2.0*	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††[b]	-1.0*	0.0
Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale††[c]	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment††	2.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] BOTOX injected into both the flexor carpi radialis and ulnaris muscles
[b] BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[c] BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of BOTOX with placebo and included 91 patients [BOTOX 360 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 27).

Table 27: Study Medication Dose and Injection Sites in Study 2 and Study 3

	Total Dose				
Muscles Injected	**BOTOX low dose (90 Units)**	**BOTOX mid dose (180 Units)**	**BOTOX high dose (360 Units)**	**Volume (mL) per site**	**Injection Sites (n)**
Wrist Flexor Carpi Ulnaris	10 Units	20 Units	40 Units	0.4	1
Flexor Carpi Radialis	15 Units	30 Units	60 Units	0.6	1
Finger Flexor Digitorum Profundus	7.5 Units	15 Units	30 Units	0.3	1
Flexor Digitorum Sublimis	7.5 Units	15 Units	30 Units	0.3	1
Elbow Biceps Brachii	50 Units	100 Units	200 Units	0.5	4

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 28.

Table 28: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2

	BOTOX low dose (90 Units) (N=21)	**BOTOX mid dose (180 Units) (N=23)**	**BOTOX high dose (360 Units) (N=21)**	**Placebo (N=26)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†b	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††c	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale††d	-0.5	-1.0*	-0.5[a]	-0.5
Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] p=0.053
[b] Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of BOTOX injected into biceps brachii muscle

Study 3 compared 3 doses of BOTOX with placebo and enrolled 88 patients [BOTOX 360 Units (N=23), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 27).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 29.

Table 29: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

	BOTOX low dose (90 Units) (N=23)	BOTOX mid dose (180 Units) (N=21)	BOTOX high dose (360 Units) (N=22)	Placebo (N=19)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale[†b]	-1.0	-1.0	-1.5[*]	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale[††c]	-1.0	-1.0	-1.0[*]	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale[†d]	-0.5	-0.5	-1.0[*]	-0.5

[†] Primary endpoint at Week 4
[††] Secondary endpoints at Week 4
[*] Significantly different from placebo ($p \leq 0.05$)
[b] Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of BOTOX injected into biceps brachii muscle

Study 4 included 170 patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose =40 Units in thumb muscles) or placebo (see Table 30). Study 5 included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, patients received 15 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus under EMG guidance (total BOTOX low dose =30 Units, total BOTOX high dose =40 Units), or placebo (see Table 30). The duration of follow-up in Study 4 and Study 5 was 12 weeks.

Table 30: Study Medication Dose and Injection Sites in Studies 4 and 5

Muscles Injected	Study 4		Study 5				Number of Injection Sites for Studies 4 and 5
	BOTOX (Units)	Volume (mL)	BOTOX low dose (Units)	BOTOX high dose (Units)	Volume low dose (mL)	Volume high dose (mL)	
Thumb Adductor Pollicis	20	0.4	15	20	0.3	0.4	1
Flexor Pollicis Longus	20	0.4	15	20	0.3	0.4	1

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 31. The MAS uses a similar scoring system as the Ashworth Scale.

Table 31: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

	BOTOX (N=66)	Placebo (N=57)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale[††a]	-1.0[*]	0.0
Median Physician Global Assessment of Response to Treatment[††]	2.0[*]	0.0

[††] Secondary endpoints at Week 6
[*] Significantly different from placebo ($p \leq 0.001$)
[a] BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function]) are presented in Table 32.

Table 32: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

	BOTOX low dose (30 Units) (N=14)	Placebo low dose (N=9)	BOTOX high dose (40 Units) (N=43)	Placebo high dose (N=23)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale[†††a]	-1.0	-1.0	-0.5[*]	0.0
Median Change from Baseline in Clinical Global Impression Score by Physician [††]	1.0	0.0	2.0[*]	0.0

[††] Secondary endpoint at Week 6
[†††] Other endpoint at Week 6
[*] Significantly different from placebo ($p \leq 0.010$)
[a] BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Lower Limb Spasticity
The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 33) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.

Table 33: Study Medication Dose and Injection Sites in Study 6

Muscles Injected	BOTOX (Units)	Number of Injection Sites
Mandatory Ankle Muscles Gastrocnemius (medial head)	75	3
Gastrocnemius (lateral head)	75	3
Soleus	75	3
Tibialis Posterior	75	3
Optional Muscles Flexor Hallucis Longus	50	2
Flexor Digitorum Longus	50	2
Flexor Digitorum Brevis	25	1
Extensor Hallucis	25	1
Rectus Femoris	100	4

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement).

Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 34).

Table 34: Co-Primary Efficacy Endpoints Results in Study 6 (Intent-to-treat Population)

	BOTOX 300 to 400 Units (N=233)	Placebo (N=235)
Mean Change from Baseline in Ankle Plantar Flexors on the modified Ashworth Scale		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7

* Significantly different from placebo ($p<0.05$)

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 11) and CGI (see Figure 12) were observed at Week 2, Week 4, and Week 6 for patients treated with BOTOX.

Figure 11: Modified Ashworth Scale Ankle Score for Study 6 – Mean Change from Baseline by Visit

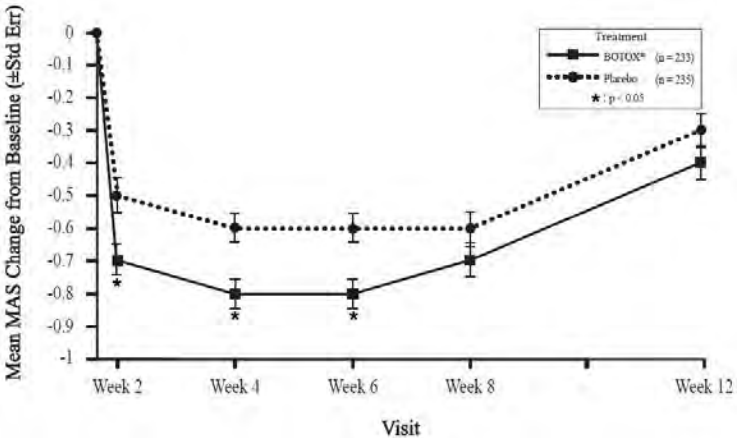
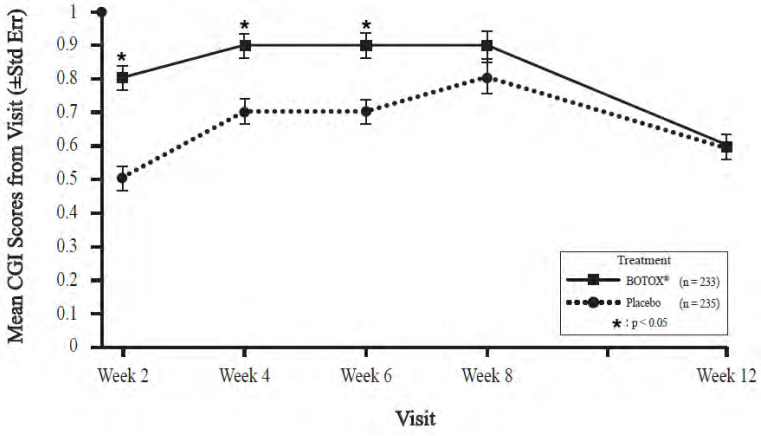


Figure 12: Clinical Global Impression by Physician for Study 6 – Mean Scores by Visit



14.5 Cervical Dystonia

A randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received BOTOX in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of BOTOX. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and

an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 35.

Table 35: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

	Placebo (N=82)	BOTOX (N=88)	95% CI on Difference
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3)[a,b]
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%)[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2)[c]
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0)[c]

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.
[c] Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 36. The total dose and muscles selected were tailored to meet individual patient needs.

Table 36: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

Muscle	Number of Patients Treated in this Muscle (N=88)	Mean % Dose per Muscle	Mid-Range of % Dose per Muscle*
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

* The mid-range of dose is calculated as the 25th to 75th percentiles.

There were several randomized studies conducted prior to the double-blind, placebo-controlled study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of BOTOX.

14.6 Primary Axillary Hyperhidrosis

The efficacy and safety of BOTOX for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities". A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group ($p<0.001$), but was not significantly different between the two BOTOX doses (see Table 37).

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in BOTOX treated patients with either dose was 201 days. Among those who received a second BOTOX injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of BOTOX (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the BOTOX group and 36% (28/78) in the placebo group, $p<0.001$. The difference in percentage of responders between BOTOX and placebo was 55% (95% CI=43.3, 65.9).

Table 37: Study 1 - Study Outcomes

Treatment Response	BOTOX 50 Units (N=104)	BOTOX 75 Units (N=110)	Placebo (N=108)	BOTOX 50-placebo (95% CI)	BOTOX 75-placebo (95% CI)
HDSS Score change ≥2 (n)[a]	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production % (n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

[a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

14.7 Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of BOTOX at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

14.8 Strabismus

Six hundred seventy-seven patients with strabismus treated with one or more injections of BOTOX were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX is supplied in a single-use vial in the following sizes:

50 Units	NDC 0023-3920-50
100 Units	NDC 0023-1145-01
200 Units	NDC 0023-3921-02

Vials of BOTOX have a holographic film on the vial label that contains the name "Allergan" within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/lot area.) If you do not see the lines of rainbow color or the name "Allergan", do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

Storage

Unopened vials of BOTOX should be stored in a refrigerator (2° to 8°C) for up to 36 months. Do not use after the expiration date on the vial. Administer BOTOX within 24 hours of reconstitution; during this period reconstituted BOTOX should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX should be clear, colorless, and free of particulate matter.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

Advise patients to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens *[see Boxed Warning and Warnings and Precautions (5.2, 5.6)]*.

Ability to Operate Machinery or Vehicles

Advise patients that if loss of strength, muscle weakness, blurred vision, dizziness, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Voiding Symptoms after Bladder Injections

After bladder injections for urinary incontinence, advise patients to contact their physician if they experience difficulties in voiding or burning sensation upon voiding.

Manufactured by:Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc. 2525 Dupont Dr. Irvine, CA 92612

Irvine, CA 92612

Footnote 8

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BELVIQ safely and effectively. See full prescribing information for BELVIQ.

BELVIQ (lorcaserin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

BELVIQ is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) (1) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes) (1)

Limitations of Use:

- The safety and efficacy of coadministration with other products for weight loss have not been established (1)
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established (1)

DOSAGE AND ADMINISTRATION

- One tablet of 10 mg twice daily (2)
- Discontinue if 5% weight loss is not achieved by week 12 (2)

DOSAGE FORMS AND STRENGTHS

10 mg film-coated tablets (3)

CONTRAINDICATIONS

Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: The safety of coadministration with other serotonergic or antidopaminergic agents has not been established. Manage with immediate BELVIQ discontinuation and provide supportive treatment. (5.1)
- Valvular heart disease: If signs or symptoms develop consider BELVIQ discontinuation and evaluate the patient for possible valvulopathy. (5.2)
- Cognitive Impairment: May cause disturbances in attention or memory. Caution with use of hazardous machinery when starting BELVIQ treatment (5.3)
- Psychiatric Disorders, including euphoria and dissociation: Do not exceed recommended dose of 10 mg twice daily (5.4)
- Monitor for depression or suicidal thoughts. Discontinue if symptoms develop. (5.4)
- Use of Antidiabetic Medications: weight loss may cause hypoglycemia. Monitor blood glucose. BELVIQ has not been studied in patients taking insulin. (5.5)
- Priapism: Patients should seek emergency treatment if an erection lasts >4 hours. Use BELVIQ with caution in patients predisposed to priapism. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (greater than 5%) in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation, and in diabetic patients are hypoglycemia, headache, back pain, cough, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or at *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Serotonergic drugs (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), triptans, bupropion, dextromethorphan, St. John's Wort): use with extreme caution due to the risk of serotonin syndrome. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Pediatric Use: Safety and effectiveness not established and use not recommended. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

[*see Dosage and Administration (2)*]

Limitations of Use:

- The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established

2 DOSAGE AND ADMINISTRATION

The recommended dose of BELVIQ is 10 mg administered orally twice daily. Do not exceed recommended dose [*see Warnings and Precautions (5.4) and Patient Counseling Information (17)*].

BELVIQ can be taken with or without food.

Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, discontinue BELVIQ, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment [*see Clinical Studies (14)*].

BMI is calculated by dividing weight (in kg) by height (in meters) squared.

A BMI chart for height in inches and weight in pounds is provided below:

Table 1. BMI Conversion Chart

Weight	(lb)	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225
	(kg)	56. 8	59. 1	61. 4	63. 6	65. 9	68. 2	70. 5	72. 7	75. 0	77. 3	79. 5	81. 8	84. 1	86. 4	88. 6	90. 9	93. 2	95. 5	97. 7	100. 0	102. 3
Height																						
(in)	(cm)																					
58	147. 3	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47
59	149. 9	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	152. 4	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	154. 9	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	157. 5	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	160. 0	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	162. 6	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	165. 1	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	167. 6	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	170. 2	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	172. 7	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	175. 3	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	177. 8	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	180. 3	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	182. 9	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	185. 4	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	188. 0	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	190. 5	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	193. 0	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

3 DOSAGE FORMS AND STRENGTHS

BELVIQ is provided as blue, film-coated, 10 mg tablets. The tablets are round, biconvex, debossed with "A" on one side and "10" on the other side.

4 CONTRAINDICATIONS

- Pregnancy [*see Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

BELVIQ is a serotonergic drug. The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists, particularly when used in combination [*see Drug Interactions (7.1)*].

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g.,

hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The safety of BELVIQ when coadministered with other serotonergic or antidopaminergic agents, including antipsychotics, or drugs that impair metabolism of serotonin, including MAOIs, has not been systematically evaluated and has not been established.

If concomitant administration of BELVIQ with an agent that affects the serotonergic neurotransmitter system is clinically warranted, extreme caution and careful observation of the patient is advised, particularly during treatment initiation and dose increases. Treatment with BELVIQ and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated [*see Adverse Reactions (6.1) and Drug Interactions (7.1)*].

5.2 Valvular Heart Disease

Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, has been reported in patients who took serotonergic drugs with 5-HT_{2B} receptor agonist activity. The etiology of the regurgitant valvular disease is thought to be activation of 5-HT_{2B} receptors on cardiac interstitial cells. At therapeutic concentrations, BELVIQ is selective for 5-HT_{2C} receptors as compared to 5-HT_{2B} receptors. In clinical trials of 1-year duration, 2.4% of patients receiving BELVIQ and 2.0% of patients receiving placebo developed echocardiographic criteria for valvular regurgitation at one year (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation): none of these patients was symptomatic [*see Adverse Reactions (6.1) see Clinical Pharmacology (12.1)*].

BELVIQ has not been studied in patients with congestive heart failure or hemodynamically-significant valvular heart disease. Preliminary data suggest that $5HT_{2B}$ receptors may be overexpressed in congestive heart failure, Therefore, BELVIQ should be used with caution in patients with congestive heart failure.

BELVIQ should not be used in combination with serotonergic and dopaminergic drugs that are potent 5-HT_{2B} receptor agonists and are known to increase the risk for cardiac valvulopathy (e.g., cabergoline).

Patients who develop signs or symptoms of valvular heart disease, including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur while being treated with BELVIQ should be evaluated and discontinuation of BELVIQ should be considered.

5.3 Cognitive Impairment

In clinical trials of at least one year in duration, impairments in attention and memory were reported adverse reactions associated with 1.9% of patients treated with BELVIQ and 0.5% of patients treated with placebo, and led to discontinuation in 0.3% and 0.1% of these patients, respectively. Other reported adverse reactions associated with BELVIQ in clinical trials included confusion, somnolence, and fatigue [*see Adverse Reactions (6.1)*].

Since BELVIQ has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BELVIQ therapy does not affect them adversely [*see Patient Counseling Information (17)*].

5.4 Psychiatric Disorders

Events of euphoria, hallucination, and dissociation were seen with BELVIQ at supratherapeutic doses in short-term studies [*see Adverse Reactions (6.1), Drug Abuse and Dependence (9.2), and Overdosage (10)*]. In clinical trials of at least 1-year in duration, 6 patients (0.2%) treated with BELVIQ developed euphoria, as compared with 1 patient (<0.1%) treated with placebo. Doses of BELVIQ should not exceed 10 mg twice a day.

Some drugs that target the central nervous system have been associated with depression or suicidal ideation. Patients treated with BELVIQ should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue BELVIQ in patients who experience suicidal thoughts or behaviors [*see Adverse Reactions (6.1)*].

5.5 Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-diabetic Therapy

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas); hypoglycemia was observed in clinical trials with BELVIQ. BELVIQ has not been studied in combination with insulin. Measurement of blood glucose levels prior to starting BELVIQ and during BELVIQ treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for anti-diabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting BELVIQ, appropriate changes should be made to the anti-diabetic drug regimen [*see Adverse Reactions (6.1)*].

5.6 Priapism

Priapism (painful erections greater than 6 hours in duration) is a potential effect of 5-HT_{2C} receptor agonism.

If not treated promptly, priapism can result in irreversible damage to the erectile tissue. Men who have an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.

BELVIQ should be used with caution in men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease). There is limited experience with the combination of BELVIQ and medication indicated for erectile dysfunction (e.g., phosphodiesterase type 5 inhibitors). Therefore, the combination of BELVIQ and these medications should be used with caution.

5.7 Heart Rate Decreases

In clinical trials of at least 1-year in duration, the mean change in heart rate (HR) was -1.2 beats per minute (bpm) in BELVIQ and -0.4 bpm in placebo-treated patients without diabetes and -2.0 beats per minute (bpm) in BELVIQ- and -0.4 bpm in placebo-treated patients with type 2 diabetes. The incidence of HR less than 50 bpm was 5.3% in BELVIQ and 3.2% in placebo-treated patients without diabetes and 3.6% in BELVIQ and 2.0% in placebo-treated patients with type 2 diabetes. In the combined population, adverse reactions of bradycardia occurred in 0.3% of BELVIQ and 0.1% of placebo-treated patients. Use with caution in patients with bradycardia or a history of heart block greater than first degree.

5.8 Hematological Changes

In clinical trials of at least one year in duration, adverse reactions of decreases in white blood cell count (including leukopenia, lymphopenia, neutropenia, and decreased white cell count) were reported in 0.4% of patients treated with BELVIQ as compared to 0.2% of patients treated with placebo. Adverse reactions of decreases in red blood cell count (including anemia and decreases in hemoglobin and hematocrit) were reported by 1.3% of patients treated with BELVIQ as compared to 1.2% treated with placebo [*see Adverse Reactions (6.1)*]. Consider periodic monitoring of complete blood count during treatment with BELVIQ.

5.9 Prolactin Elevation

Lorcaserin moderately elevates prolactin levels. In a subset of placebo-controlled clinical trials of at least one year in duration, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, measured both before and 2 hours after dosing, occurred in 6.7%, 1.7%, and 0.1% of BELVIQ-treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively [*see Adverse Reactions (6.1)*]. Prolactin should be measured when symptoms and signs of prolactin excess are suspected (e.g., galactorrhea, gynecomastia). There was one patient treated with BELVIQ who developed a prolactinoma during the trial. The relationship of BELVIQ to the prolactinoma in this patient is unknown.

5.10 Pulmonary Hypertension

Certain centrally-acting weight loss agents that act on the serotonin system have been associated with pulmonary hypertension, a rare but lethal disease. Because of the low incidence of this disease, the clinical trial experience with BELVIQ is inadequate to determine if BELVIQ increases the risk for pulmonary hypertension.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in labeling:

- Serotonin Syndrome or NMS-like Reactions [*see Warnings and Precautions (5.1)*]
- Valvular Heart Disease [*see Warnings and Precautions (5.2)*]
- Cognitive Impairment [*see Warnings and Precautions (5.3)*]
- Psychiatric Disorders [*see Warnings and Precautions (5.4)*]
- Hypoglycemia [*see Warnings and Precautions (5.5)*]
- Heart Rate Decreases [*see Warnings and Precautions (5.7)*]
- Hematological Changes [*see Warnings and Precautions (5.8)*]
- Prolactin Elevation [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

In the BELVIQ placebo-controlled clinical database of trials of at least one year in duration, of 6888 patients (3451 BELVIQ vs. 3437 placebo; age range 18-66 years, 79.3% women, 66.6% Caucasians, 19.2% Blacks, 11.8% Hispanics, 2.4% other, 7.4% type 2 diabetics), a total of 1969 patients were exposed to BELVIQ 10 mg twice daily for 1 year and 426 patients were exposed for 2 years.

In clinical trials of at least one year in duration, 8.6% of patients treated with BELVIQ prematurely discontinued treatment due to adverse reactions, compared with 6.7% of placebo-treated patients. The most

common adverse reactions leading to discontinuation more often among BELVIQ treated patients than placebo were headache (1.3% vs. 0.8%), depression (0.9% vs. 0.5%) and dizziness (0.7% vs. 0.2%).

Most Common Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions for non-diabetic patients (greater than 5% and more commonly than placebo) treated with BELVIQ compared to placebo were headache, dizziness, fatigue, nausea, dry mouth, and constipation. The most common adverse reactions for diabetic patients were hypoglycemia, headache, back pain, cough, and fatigue. Adverse reactions that were reported by greater than or equal to 2% of patients and were more frequently reported by patients taking BELVIQ compared to placebo are summarized in Table 2 (non-diabetic subjects) and Table 3 (subjects with type 2 diabetes mellitus).

Table 2. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients without Diabetes Mellitus

	Number of patients (%)	
Adverse Reaction	**BELVIQ 10 mg BID N=3195**	**Placebo N=3185**
Gastrointestinal Disorders		
Nausea	264 (8.3)	170 (5.3)
Diarrhea	207 (6.5)	179 (5.6)
Constipation	186 (5.8)	125 (3.9)
Dry mouth	169 (5.3)	74 (2.3)
Vomiting	122 (3.8)	83 (2.6)
General Disorders And Administration Site Conditions		
Fatigue	229 (7.2)	114 (3.6)
Infections And Infestations		
Upper respiratory tract infection	439 (13.7)	391 (12.3)
Nasopharyngitis	414 (13.0)	381 (12.0)
Urinary tract infection	207 (6.5)	171 (5.4)
Musculoskeletal And Connective Tissue Disorders		
Back pain	201 (6.3)	178 (5.6)
Musculoskeletal pain	65 (2.0)	43 (1.4)
Nervous System Disorders		
Headache	537 (16.8)	321 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	136 (4.3)	109 (3.4)
Oropharyngeal pain	111 (3.5)	80 (2.5)
Sinus congestion	93 (2.9)	78 (2.4)
Skin And Subcutaneous Tissue Disorders		
Rash	67 (2.1)	58 (1.8)

Table 3. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients with Type 2 Diabetes Mellitus

	Number of patients (%)	
Adverse Reaction	**BELVIQ 10 mg BID N=256**	**Placebo N=252**
Gastrointestinal Disorders		
Nausea	24 (9.4)	20 (7.9)
Toothache	7 (2.7)	0
General Disorders And Administration Site Conditions		
Fatigue	19 (7.4)	10 (4.0)
Peripheral edema	12 (4.7)	6 (2.4)
Immune System Disorders		
Seasonal allergy	8 (3.1)	2 (0.8)
Infections And Infestations		
Nasopharyngitis	29 (11.3)	25 (9.9)
Urinary tract infection	23 (9.0)	15 (6.0)
Gastroenteritis	8 (3.1)	5 (2.0)
Metabolism And Nutrition Disorders		
Hypoglycemia	75 (29.3)	53 (21.0)
Worsening of diabetes mellitus	7 (2.7)	2 (0.8)
Decreased appetite	6 (2.3)	1 (0.4)
Musculoskeletal And Connective Tissue Disorders		
Back pain	30 (11.7)	20 (7.9)
Muscle spasms	12 (4.7)	9 (3.6)
Nervous System Disorders		
Headache	37 (14.5)	18 (7.1)
Dizziness	18 (7.0)	16 (6.3)
Psychiatric Disorders		
Anxiety	9 (3.5)	8 (3.2)
Insomnia	9 (3.5)	6 (2.4)
Stress	7 (2.7)	3 (1.2)
Depression	6 (2.3)	5 (2.0)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	21 (8.2)	11 (4.4)
Vascular Disorders		
Hypertension	13 (5.1)	8 (3.2)

Other Adverse Reactions

Serotonin-associated Adverse Reactions

SSRIs, SNRIs, bupropion, tricyclic antidepressants, and MAOIs were excluded from the BELVIQ trials. Triptans and dextromethorphan were permitted: 2% and 15%, respectively, of patients without diabetes and 1% and 12%, respectively, of patients with type 2 diabetes experienced concomitant use at some point during the trials. Two patients treated with BELVIQ in the clinical program experienced a constellation of symptoms and signs consistent with serotonergic excess, including one patient on concomitant dextromethorphan who reported an event of serotonin syndrome. Some symptoms of possible serotonergic etiology that are included in the criteria for serotonin syndrome were reported by patients treated with BELVIQ and placebo during clinical trials of at least 1 year in duration. In both groups, chills were the most frequent of these events (1.0% vs. 0.2%, respectively), followed by tremor (0.3% vs. 0.2%), confusional state (0.2% vs. less than 0.1%), disorientation (0.1% vs. 0.1%) and hyperhidrosis (0.1% vs. 0.2%). Because serotonin syndrome has a very low incidence, an

association between BELVIQ and serotonin syndrome cannot be excluded on the basis of clinical trial results [*see Warnings and Precautions (5.1)*].

Hypoglycemia in Patients with Type 2 Diabetes

In a clinical trial of patients with type 2 diabetes mellitus, hypoglycemia requiring the assistance of another person occurred in 4 (1.6%) of BELVIQ-treated patients and in 1 (0.4%) placebo-treated patient. Of these 4 BELVIQ-treated patients, all were concomitantly using a sulfonylurea (with or without metformin). BELVIQ has not been studied in patients taking insulin. Hypoglycemia defined as blood sugar less than or equal to 65 mg/dL and with symptoms occurred in 19 (7.4%) BELVIQ-treated patients and 16 (6.3%) placebo-treated patients.

Cognitive Impairment

In clinical trials of at least 1-year duration, adverse reactions related to cognitive impairment (e.g., difficulty with concentration/attention, difficulty with memory, and confusion) occurred in 2.3% of patients taking BELVIQ and 0.7% of patients taking placebo.

Psychiatric Disorders

Psychiatric disorders leading to hospitalization or drug withdrawal occurred more frequently in patients treated with BELVIQ (2.2%) as compared to placebo (1.1%) in non-diabetic patients.

Euphoria. In short-term studies with healthy individuals, the incidence of euphoric mood following supratherapeutic doses of BELVIQ (40 and 60 mg) was increased as compared to placebo [*see Drug Abuse and Dependence (9.2)*]. In clinical trials of at least 1-year duration in obese patients, euphoria was observed in 0.17% of patients taking BELVIQ and 0.03% taking placebo.

Depression and Suicidality. In trials of at least one year in duration, reports of depression/mood problems occurred in 2.6% BELVIQ-treated vs. 2.4% placebo-treated and suicidal ideation occurred in 0.6% BELVIQ-treated vs. 0.4% placebo-treated patients. 1.3% of BELVIQ patients vs. 0.6% of placebo patients discontinued drug due to depression-, mood-, or suicidal ideation-related events.

Laboratory Abnormalities

Lymphocyte and Neutrophil Counts. In clinical trials of at least 1-year duration, lymphocyte counts were below the lower limit of normal in 12.2% of patients taking BELVIQ and 9.0% taking placebo, and neutrophil counts were low in 5.6% and 4.3%, respectively.

Hemoglobin. In clinical trials of at least 1-year duration, 10.4% of patients taking BELVIQ and 9.3% taking placebo had hemoglobin below the lower limit of normal at some point during the trials.

Prolactin. In clinical trials, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, occurred in 6.7%, 1.7%, and 0.1% of BELVIQ-treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively.

Eye disorders.

More patients on BELVIQ reported an eye disorder than patients on placebo in clinical trials of patients without diabetes (4.5% vs. 3.0%) and with type 2 diabetes (6.3% vs. 1.6%). In the population without diabetes, events of blurred vision, dry eye, and visual impairment occurred in BELVIQ-treated patients at an incidence greater than that of placebo. In the population with type 2 diabetes, visual disorders, conjunctival infections, irritations, and inflammations, ocular sensation disorders, and cataract conditions occurred in BELVIQ-treated patients at an incidence greater than placebo.

Echocardiographic Safety Assessments

The possible occurrence of regurgitant cardiac valve disease was prospectively evaluated in 7794 patients in three clinical trials of at least one year in duration, 3451 of whom took BELVIQ 10 mg twice daily. The primary echocardiographic safety parameter was the proportion of patients who developed echocardiographic criteria of mild or greater aortic insufficiency and/or moderate or greater mitral insufficiency from baseline to 1 year. At 1 year, 2.4% of patients who received BELVIQ and 2.0% of patients who received placebo developed valvular regurgitation. The relative risk for valvulopathy with BELVIQ is summarized in Table 4. BELVIQ was not studied in patients with congestive heart failure or hemodynamically-significant valvular heart disease [*see Warnings and Precautions (5.2)*].

Table 4. Incidence of FDA-Defined Valvulopathy at Week 52 by Treatment Group[1]

	Study 1		Study 2		Study 3	
	BELVIQ N=1278	**Placebo N=1191**	**BELVIQ N=1208**	**Placebo N=1153**	**BELVIQ N=210**	**Placebo N=209**
FDA-defined Valvulopathy, n (%)	34 (2.7)	28 (2.4)	24 (2.0)	23 (2.0)	6 (2.9)	1 (0.5)
Relative Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)		5.97 (0.73, 49.17)	
Pooled RR (95% CI)	**1.16 (0.81, 1.67)**					

[1] Patients without valvulopathy at baseline who received study medication and had a post-baseline echocardiogram; ITT-intention-to-treat; LOCF-last observation carried forward

7 DRUG INTERACTIONS

7.1 Use with Other Agents that Affect Serotonin Pathways

Based on the mechanism of action of BELVIQ and the theoretical potential for serotonin syndrome, use with extreme caution in combination with other drugs that may affect the serotonergic neurotransmitter systems, including, but not limited to, triptans, monoamine oxidase inhibitors (MAOIs, including linezolid, an antibiotic which is a reversible non-selective MAOI), selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), dextromethorphan, tricyclic antidepressants (TCAs), bupropion, lithium, tramadol, tryptophan, and St. John's Wort [*see Warnings and Precautions (5.1)*].

7.2 Cytochrome P450 (2D6) substrates

Use caution when administering BELVIQ together with drugs that are CYP 2D6 substrates, as BELVIQ can increase exposure of these drugs [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X.

Risk Summary

BELVIQ is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. Maternal exposure to lorcaserin in late pregnancy in rats resulted in lower body weight in offspring which persisted to adulthood. If this drug is used during pregnancy, or if the patient

becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of maternal weight loss to the fetus.

Clinical Considerations
A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Animal Data
Reproduction studies were performed in pregnant rats and rabbits that were administered lorcaserin during the period of embryofetal organogenesis. Plasma exposures up to 44 and 19 times human exposure in rats and rabbits, respectively, did not reveal evidence of teratogenicity or embryolethality with lorcaserin hydrochloride.

In a pre- and postnatal development study, maternal rats were dosed from gestation through post-natal day 21 at 5, 15, and 50mg/kg lorcaserin; pups were indirectly exposed *in utero* and throughout lactation. The highest dose (~44 times human exposure) resulted in stillborns and lower pup viability. All doses lowered pup body weight similarly at birth which persisted to adulthood; however, no developmental abnormalities were observed and reproductive performance was not affected at any dose.

8.3 Nursing Mothers

It is not known whether BELVIQ is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BELVIQ in pediatric patients below the age of 18 have not been established and the use of BELVIQ is not recommended in pediatric patients.

8.5 Geriatric Use

In the BELVIQ clinical trials, a total of 135 (2.5%) of the patients were 65 years of age and older. Clinical studies of BELVIQ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Since elderly patients have a higher incidence of renal impairment, use of BELVIQ in the elderly should be made on the basis of renal function [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. Elderly patients with normal renal function should require no dose adjustment.

8.6 Renal Impairment

No dose adjustment of BELVIQ is required in patients with mild renal impairment. Use BELVIQ with caution in patients with moderate renal impairment. Use of BELVIQ in patients with severe renal impairment or end stage renal disease is not recommended [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Dose adjustment is not required for patients with mild hepatic impairment (Child-Pugh score 5-6) to moderate hepatic impairment (Child-Pugh score 7-9). The effect of severe hepatic impairment on lorcaserin was not

evaluated. Use lorcaserin with caution in patients with severe hepatic impairment [*see Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

In a human abuse potential study in recreational drug abusers, supratherapeutic oral doses of lorcaserin (40 and 60 mg) produced up to two- to six-fold increases on measures of "High", "Good Drug Effects", "Hallucinations" and "Sedation" compared to placebo. These responses were similar to those produced by oral administration of the positive control drugs, zolpidem (15 and 30 mg) and ketamine (100 mg). In this study, the incidence of the adverse reaction of euphoria following lorcaserin administration (40 and 60 mg; 19%) is similar to the incidence following zolpidem administration (13-16%), but less than the incidence following ketamine administration (50%). The duration of euphoria following lorcaserin administration persisted longer (> 9 hours) than that following zolpidem (1.5 hours) or ketamine (2.5 hours) administration.

Overall, in short-term studies with healthy individuals, the rate of euphoria following oral administration of lorcaserin was 16% following 40 mg (n = 11 of 70) and 19% following 60 mg (n = 6 of 31). However, in clinical studies with obese patients with durations of 4 weeks to 2 years, the incidence of euphoria and hallucinations following oral doses of lorcaserin up to 40 mg was low (< 1.0%).

9.3 Dependence

There are no data from well-conducted animal or human studies that evaluate whether lorcaserin can induce physical dependence, as evidenced by a withdrawal syndrome. However, the ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses at supratherapeutic doses suggests that lorcaserin may produce psychic dependence.

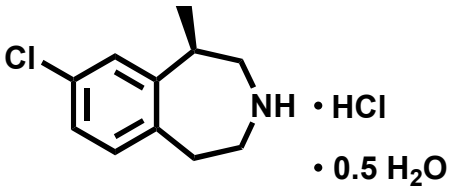
10 OVERDOSAGE

No experience with overdose of BELVIQ is available. In clinical studies that used doses that were higher than the recommended dose, the most frequent adverse reactions associated with BELVIQ were headache, nausea, abdominal discomfort, and dizziness. Single 40- and 60-mg doses of BELVIQ caused euphoria, altered mood, and hallucination in some subjects. Treatment of overdose should consist of BELVIQ discontinuation and general supportive measures in the management of overdosage. BELVIQ is not eliminated to a therapeutically significant degree by hemodialysis.

11 DESCRIPTION

BELVIQ (lorcaserin hydrochloride) is a serotonin 2C receptor agonist for oral administration used for chronic weight management. Its chemical name is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate. The empirical formula is $C_{11}H_{15}Cl_2N \cdot 0.5H_2O$, and the molecular weight of the hemihydrate form is 241.16 g/mol.

The structural formula is:



Lorcaserin hydrochloride hemihydrate is a white to off-white powder with solubility in water greater than 400 mg/mL. Each BELVIQ tablet contains 10.4 mg of crystalline lorcaserin hydrochloride hemihydrate, equivalent to 10.0 mg anhydrous lorcaserin hydrochloride, and the following inactive ingredients: silicified microcrystalline cellulose; hydroxypropyl cellulose NF; croscarmellose sodium NF; colloidal silicon dioxide NF, polyvinyl alcohol USP, polyethylene glycol NF, titanium dioxide USP, talc USP, FD&C Blue #2 aluminum lake, and magnesium stearate NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lorcaserin is believed to decrease food consumption and promote satiety by selectively activating 5-HT_{2C} receptors on anorexigenic pro-opiomelanocortin neurons located in the hypothalamus. The exact mechanism of action is not known.

Lorcaserin at the recommended daily dose selectivity interacts with 5-HT_{2C} receptors as compared to 5-HT_{2A} and 5-HT_{2B} receptors (see Table 5), other 5-HT receptor subtypes, the 5-HT receptor transporter, and 5-HT reuptake sites.

Table 5. Lorcaserin Potency (EC50) and Binding Affinity (Ki) to Human 5-$HT2_A$, 5-$HT2_B$, and 5-$HT2_C$ Receptor Subtypes

Serotonin Receptor Subtype	EC_{50}, nM	Ki, nM
$5HT_{2C}$	39	13
$5HT_{2B}$	2380	147
$5HT_{2A}$	553	92

12.2 Pharmacodynamics

Cardiac Electrophysiology. The effect of multiple oral doses of lorcaserin 15 mg and 40 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg) controlled four-treatment arm parallel thorough QT study in 244 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern.

12.3 Pharmacokinetics

Absorption

Lorcaserin is absorbed from the gastrointestinal tract with peak plasma concentration occurring 1.5 - 2 hours after oral dosing. The absolute bioavailability of lorcaserin has not been determined. Lorcaserin has a plasma half life of ~11 hours; steady state is reached within 3 days after twice daily dosing, and accumulation is estimated to be approximately 70%.

Effect of Food. Twelve adult volunteers (6 men and 6 women) were given a single 10 mg oral dose of BELVIQ in a fasted state and after administration of a high fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal. The C_{max} increased approximately 9% and exposure (AUC) increased approximately 5% under fed conditions. T_{max} was delayed approximately 1 hour in the fed state. BELVIQ can be administered with or without food.

Distribution

Lorcaserin distributes to the cerebrospinal fluid and central nervous system in humans. Lorcaserin hydrochloride is moderately bound (~70%) to human plasma proteins.

Metabolism

Lorcaserin is extensively metabolized in the liver by multiple enzymatic pathways. After oral administration of BELVIQ, the major circulating metabolite is lorcaserin sulfamate (M1), with a plasma C_{max} that exceeds lorcaserin C_{max} by 1- to 5-fold. *N*-carbamoyl glucuronide lorcaserin (M5) is the major metabolite in urine; M1 is a minor metabolite in urine, representing approximately 3% of dose. Other minor metabolites excreted in urine were identified as glucuronide or sulfate conjugates of oxidative metabolites. The principal metabolites exert no pharmacological activity at serotonin receptors.

Elimination

Lorcaserin is extensively metabolized by the liver and the metabolites are excreted in the urine. In a human mass balance study in which healthy subjects ingested radiolabeled lorcaserin, 94.5% of radiolabeled material was recovered, with 92.3% and 2.2% recovered from urine and feces, respectively.

Specific Populations

Renal Impairment. The disposition of lorcaserin was studied in patients with varying degrees of renal function. Creatinine clearance (CLcr) was calculated by Cockgroft-Gault equation based on ideal body weight (IBW). Impaired renal function decreased C_{max} of lorcaserin, with no change in AUC.

Exposure of lorcaserin sulfamate metabolite (M1) was increased in patients with impaired renal function by approximately 1.7-fold in mild (CLcr = 50-80 mL/min), 2.3-fold in moderate (CLcr = 30-50 mL/min) and 10.5-fold in severe renal impairment (CLcr = <30 mL/min) compared to normal subjects (CLcr >80 mL/min).

Exposure of the N-carbamoyl-glucuronide metabolite (M5) was increased in patients with impaired renal function by approximately 1.5-fold in mild (CLcr = 50-80 mL/min), 2.5-fold in moderate (CLcr = 30-50 mL/min) and 5.1-fold in severe renal impairment (CLcr = <30 mL/min) compared to normal subjects (CLcr >80 mL/min).

The terminal half-life of M1 is prolonged by 26%, 96%, and 508% in mild, moderate, and severe renal impairment, respectively. The terminal half-life of M5 is prolonged by 0%, 26%, and 22% in mild, moderate,

and severe renal impairment, respectively. The metabolites M1 and M5 accumulate in patients with severely impaired renal function.

Approximately 18% of metabolite M5 in the body was cleared from the body during a standard 4-hour hemodialysis procedure. Lorcaserin and M1 were not cleared by hemodialysis. Lorcaserin is not recommended for patients with severe renal impairment (CLcr <30 mL/min) or patients with end stage renal disease [*see Use in Specific Populations (8.6)*].

Estimate Ideal Body Weight (IBW) in (kg)

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

The Cockroft-Gault calculation using the IBW:

female:

$$\text{GFR (mL/min)} = 0.85 \times \frac{(140 - \text{age}) \times \text{ideal body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

male:

$$\text{GFR (mL/min)} = \frac{(140 - \text{age}) \times \text{ideal body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Hepatic Impairment. The disposition of lorcaserin was evaluated in patients with hepatic impairment and subjects with normal hepatic function. Lorcaserin C_{max} was 7.8% and 14.3% lower, in subjects with mild (Child-Pugh score 5-6) and moderate (Child-Pugh score 7-9) hepatic impairment, respectively, than that in subjects with normal hepatic function. The half-life of lorcaserin is prolonged by 59% to 19 hours in patients with moderate hepatic impairment. Lorcaserin exposure (AUC) is approximately 22% and 30% higher in patients with mild and moderate hepatic impairment, respectively. Dose adjustment is not required for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on lorcaserin was not evaluated [*see Use in Specific Populations (8.7)*].

Gender. No dosage adjustment based on gender is necessary. Gender did not meaningfully affect the pharmacokinetics of lorcaserin.

Geriatric. No dosage adjustment is required based on age alone. In a clinical trial of 12 healthy elderly (age greater than 65 years) subjects and 12 matched adult patients, lorcaserin exposure (AUC and C_{max}) was equivalent in the two groups. C_{max} was approximately 18% lower in the elderly group, and T_{max} was increased from 2 hours to 2.5 hours in the elderly group as compared to the non-elderly adult group.

Race. No dosage adjustment based on race is necessary. Race did not meaningfully affect the pharmacokinetics of lorcaserin.

Drug-Drug Interactions

Lorcaserin inhibits CYP 2D6-mediated metabolism. In a clinical trial in 21 CYP 2D6 extensive metabolizers, concomitant administration of lorcaserin (10 mg BID for 4 days) increased dextromethorphan peak concentrations (C_{max}) by approximately 76% and exposure (AUC) by approximately 2-fold [*see Drug Interactions (7.2)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis

Lorcaserin hydrochloride was not mutagenic in an *in vitro* bacterial mutation assay (Ames test), was not clastogenic in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells, and was not genotoxic in an *in vivo* micronucleus assay in rat bone marrow.

Carcinogenesis

The carcinogenic potential of lorcaserin hydrochloride was assessed in two-year carcinogenicity studies in mice and rats. CD-1 mice received doses of 5, 25 and 50 mg/kg. There were no treatment-related increases in the incidence of any tumor in mice at doses that produced plasma exposure in males and females of 8 and 4-times the daily human clinical dose, respectively.

In the rat carcinogenicity study, male and female Sprague-Dawley rats received 10, 30, and 100 mg/kg lorcaserin hydrochloride. In females, mammary adenocarcinoma increased at 100 mg/kg, which was associated with plasma exposures that were 87-times the daily human clinical dose. The incidence of mammary fibroadenoma was increased in female rats at all doses with no safety margin to the clinical dose. The increases in adenocarcinomas and fibroadenomas may be associated with lorcaserin hydrochloride-induced changes in prolactin homeostasis in rats. The relevance of the increased incidence of mammary adenocarcinomas and fibroadenomas in rats to humans is unknown.

In male rats, treatment-related neoplastic changes were observed in the subcutis (fibroadenoma, Schwannoma), the skin (squamous cell carcinoma), mammary gland (adenocarcinoma and fibroadenoma), and the brain (astrocytoma) at greater than or equal to 30 mg/kg (plasma exposure 17-times human clinical dose). At higher exposure, liver adenoma and thyroid follicular cell adenoma were increased but were considered secondary to liver enzyme induction in rats and are not considered relevant to humans. Human brain exposure ($AUC_{24h,ss}$) to lorcaserin at the clinical dose is estimated to be 70-fold lower than brain exposure in rats at the dose at which no increased incidence of astrocytoma was observed. Excluding the liver and thyroid tumors, these neoplastic findings in male rats are of unknown relevance to humans.

Impairment of Fertility

Potential effects on fertility were assessed in Sprague-Dawley rats in which males were dosed with lorcaserin hydrochloride for 4 weeks prior to and through the mating period, and females were dosed for 2 weeks prior to mating and through gestation day 7. Lorcaserin hydrochloride had no effects on fertility in rats at exposures up to 29 times the human clinical dose.

14 CLINICAL STUDIES

The safety and efficacy of BELVIQ for chronic weight management in conjunction with reduced caloric intake and increased physical activity were evaluated in 3 randomized, double-blind, placebo-controlled trials with durations ranging from 52 to 104 weeks. Two trials in adults without type 2 diabetes mellitus (Study 1 and Study 2) and one study in adults with type 2 diabetes mellitus (Study 3) evaluated the effect of BELVIQ 10 mg twice daily. The primary efficacy parameter in these studies was weight loss at 1 year, which was assessed by percent of patients achieving greater than or equal to 5% weight loss, percent of patients achieving greater than or equal to 10% weight loss, and mean weight change. All patients received one-on-one instruction for a

reduced-calorie diet and exercise counseling that began with the first dose of study medication and continued every four weeks throughout the trial.

Study 1 was a 2-year study that enrolled 3182 patients who were obese (BMI 30-45 kg/m^2), or who were overweight (BMI 27-29.9 kg/m^2) and had at least one weight-related comorbid condition such as hypertension or dyslipidemia. In Year 2, placebo patients were continued on placebo and BELVIQ patients were re-randomized in a 2:1 ratio to continue BELVIQ or to switch to placebo. The mean age was 44 (range 18-65); 83.5% were women. Sixty-seven percent were Caucasian, 19% were African American and 12% were Hispanic. Mean baseline body weight was 100.0 kg and mean BMI was 36.2 kg/m^2.

Study 2 was a 1-year study that enrolled 4008 patients who were obese (BMI 30-45 kg/m^2) or were overweight (BMI 27-29.9 kg/m^2) with at least one comorbid condition such as hypertension or dyslipidemia. The mean age was 44 (range 18-65); 80% were women. Sixty-seven percent were Caucasian, 20% were African American and 11% were Hispanic. Mean baseline body weight was 100.2 kg and mean BMI was 35.9 kg/m^2.

Study 3 was a 1-year study that enrolled 604 adult patients with BMI greater than or equal to 27 kg/m^2 and inadequately controlled type 2 diabetes (HbA1c range 7-10%) being treated with metformin and/or a sulfonylurea. Mean age was 53 (range 21-65); 54% were women. Sixty-one percent were Caucasian, 21% African American and 14% were Hispanic. Mean BMI was 36 kg/m^2 and mean HbA1C was 8.1%.

A substantial percentage of randomized subjects withdrew from each study prior to week 52: 50% in Study 1, 45% in Study 2 and 36% in Study 3.

One-Year Weight Management in Patients without Diabetes Mellitus

Weight loss at 1 year in Studies 1 and 2 is presented in Table 6. The pooled data are reflective of the individual study results.

Statistically significantly greater weight loss was achieved with BELVIQ compared to placebo at week 52. The Year 1 placebo-adjusted weight loss achieved in patients treated with BELVIQ was 3.3 kg by ITT/LOCF analysis. The time course of weight loss with BELVIQ and placebo through week 52 is depicted in Figure 1.

Patients who did not lose at least 5% of baseline body weight by week 12 were unlikely to achieve at least 5% weight loss at week 52.

Table 6. Weight Loss at 1 Year in Studies 1 and 2 Combined

	BELVIQ 10 mg BID N=3098	Placebo N=3038
Weight (kg)		
Baseline mean (SD)	100.4 (15.7)	100.2 (15.9)
Change from baseline (adjusted mean[1]) (SE)	-5.8 (0.1)	-2.5 (0.1)
Difference from placebo (adjusted mean[1]) (95% CI)	-3.3** (-3.6, -2.9)	
Percent change from baseline (adjusted mean[1]) (SE)	-5.8 (0.1)	-2.5 (0.1)
Difference from placebo (adjusted mean[1]) (95% CI)	-3.3** (-3.6, -3.0)	
% of Patients losing greater than or equal to 5% body weight	47.1	22.6
Difference from placebo (95% CI)	24.5** (22.2, 26.8)	
% of Patients losing greater than or equal to 10% body weight	22.4	8.7
Difference from placebo (95% CI)	13.8** (12.0, 15.5)	

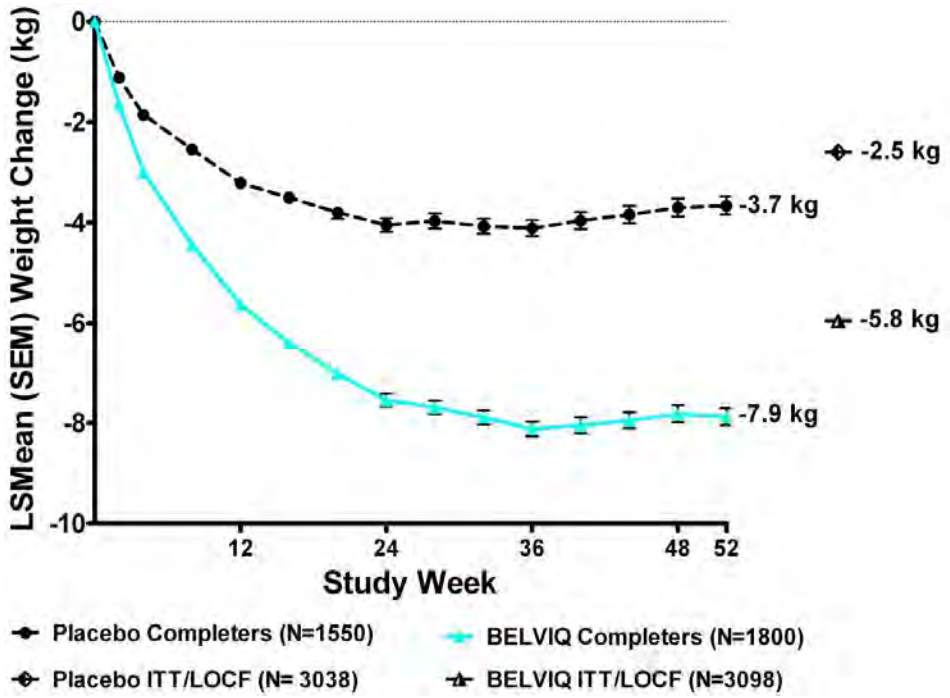
SD=Standard Deviation; SE=Standard Error; CI=Confidence Interval

Intent to Treat Population using last observation carried forward method; All patients who received study medication and had a post-baseline body weight. Forty-four percent (44%) of patients in Belviq and 51% in placebo dropped out before the 52-week endpoint.

[1]Least squares means adjusted for baseline value, treatment, study and treatment by study interaction.

**p<0.001 compared to placebo. Type 1 error was controlled across the three endpoints.

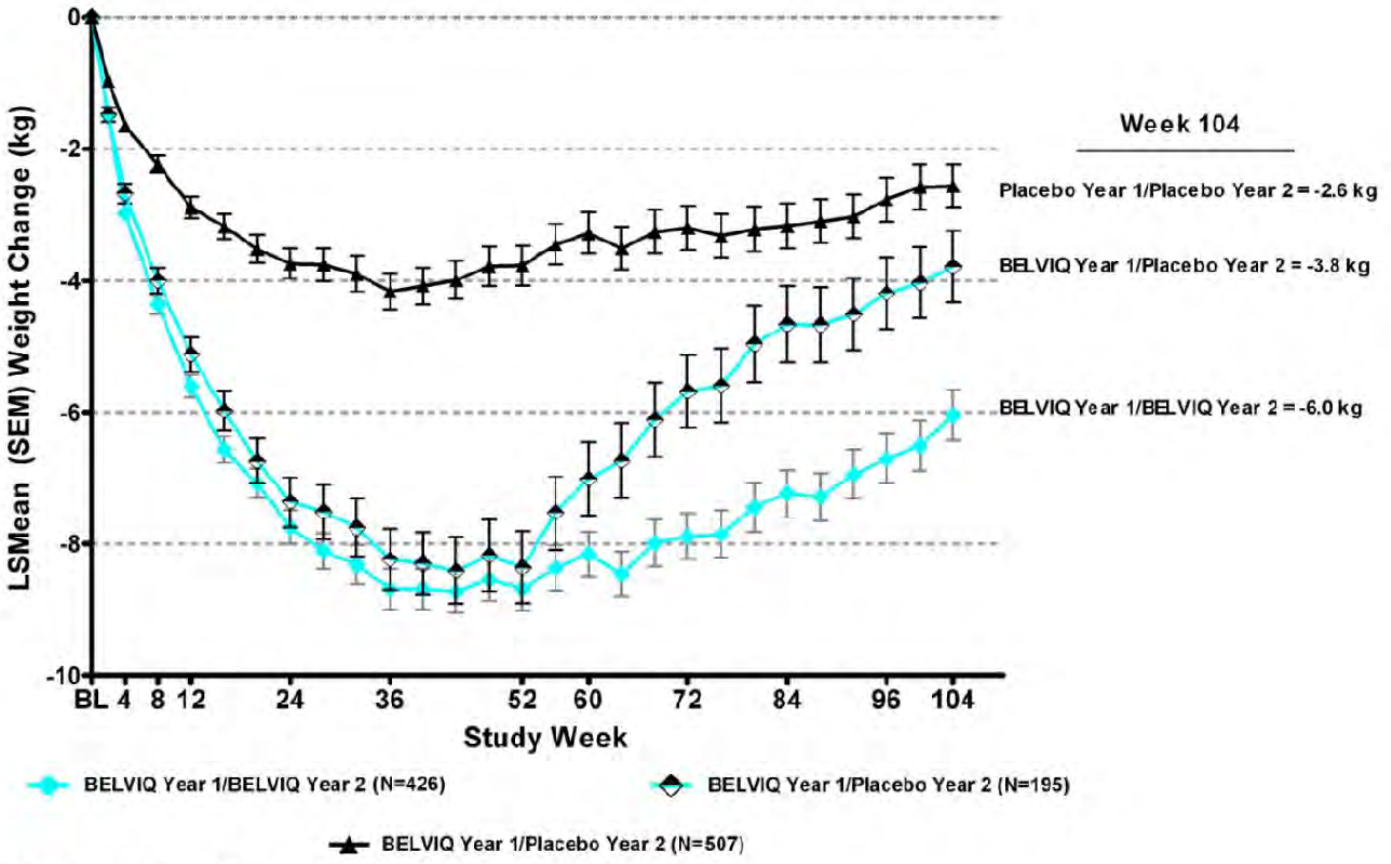
Figure 1. Longitudinal Weight Change (kg) in Completer Population: Studies 1 and 2



Two-Year Weight Management in Patients without Diabetes Mellitus

The safety and efficacy of BELVIQ for weight management during 2 years of treatment were evaluated in Study 1. Of the 3182 patients who were randomized in Year 1, 1553 (48.8%) were randomized in Year 2. Patients in all three Year 2 patient groups (BELVIQ Year 1/ BELVIQ Year 2, BELVIQ Year 1/placebo Year 2, and placebo Year 1/placebo Year 2) regained weight in Year 2 but remained below their Year 1 mean baseline weight (Figure 2).

Figure 2. Body Weight Changes during Study 1 in the Completers Population



Year 1 Randomized: BELVIQ N=1595, Placebo N=1587

Year 2 Randomized: BELVIQ Year 1/BELVIQ Year 2, N=573; BELVIQ Year 1/Placebo Year 2, N=283; Placebo Year 1/Placebo Year 2, N=697

Effect of BELVIQ on Cardiometabolic Parameters and Anthropometry

Changes in lipids, fasting glucose, fasting insulin, waist circumference, heart rate, and blood pressure with BELVIQ are shown in Table 7.

In a substudy of 154 patients conducted as part of Study 2, DEXA analysis showed a 9.9% reduction in fat mass from a baseline of 45.0 kg in patients treated with BELVIQ compared to a 4.6% reduction from a baseline of 44.5 kg in patients treated with placebo. The placebo-adjusted reduction in fat mass achieved on BELVIQ was -5.3%. Reductions in lean body mass were 1.9% and 0.3% from baseline values of 48.0 kg and 51.0 kg, respectively, for BELVIQ- and placebo-treated patients.

Table 7. Mean Changes in Cardiometabolic Parameters and Waist Circumference in Year 1 of Studies 1 and 2

	BELVIQ N=3096		Placebo N=3039		
	Baseline mg/dL	**% change from Baseline (LSMean[1])**	**Baseline mg/dL**	**% change from Baseline (LSMean)**	**BELVIQ minus Placebo (LSMean)**
Total Cholesterol	194.4	-0.9	194.8	0.4	-1.2*
LDL Cholesterol	114.3	1.6	114.1	2.9	-1.3*
HDL Cholesterol	53.2	1.8	53.5	0.6	1.2*
Triglycerides	135.4	-5.3	137.0	-0.5	-4.8*
	Baseline	**change from Baseline (LSMean)**	**Baseline**	**change from Baseline (LSMean)**	**BELVIQ minus Placebo (LSMean)**
Systolic blood pressure (mmHg)	121.4	-1.8	121.5	-1.0	-0.7*
Diastolic blood pressure (mmHg)	77.4	-1.6	77.7	-1.0	-0.6*
Heart Rate (bpm)	69.5	-1.2	69.5	-0.4	-0.8
Fasting glucose (mg/dL)	92.1	-0.2	92.4	0.6	-0.8
Fasting insulin[2] (µIU/mL)	15.9	-3.3	15.8	-1.3	-2.1*
Waist Circumference (cm)	109.3	-6.6	109.6	-4.0	-2.5

[1] Least squares means adjusted for baseline value, treatment, study and treatment by study interaction

[2] Measured in Study 1 only (n=1538)

* Statistically significant versus placebo based on the pre-specified gatekeeping method for controlling Type I error in key secondary endpoints.

One-Year Weight Management in Patients with Type 2 Diabetes Mellitus

Weight loss among patients with type 2 diabetes mellitus who were treated with BELVIQ was statistically significantly greater than that among patients treated with placebo (Table 8).

Table 8. Weight Loss at 1 Year in Study 3 (Type 2 Diabetes Mellitus)

	BELVIQ 10 mg BID N=251	Placebo N=248
Weight loss (kg)		
Baseline mean (SD)	103.5 (17.2)	102.3 (18.0)
Change from baseline (adjusted mean[1]) (SE)	-4.7 (0.4)	-1.6 (0.4)
Difference from placebo (adjusted mean[1])	-3.1**	
(95% CI)	(-4.0, -2.2)	
Percent change from baseline (adjusted mean[1]) (SE)	-4.5 (0.4)	-1.5 (0.4)
Difference from placebo (adjusted mean[1])	-3.1**	
(95% CI)	(-3.9, -2.2)	
% of Patients losing greater than or equal to 5% body weight	37.5	16.1
Difference from placebo	21.3**	
(95% CI)	(13.8, 28.9)	
% of Patients losing greater than or equal to 10% body weight	16.3	4.4
Difference from placebo	11.9**	
(95% CI)	(6.7, 17.1)	

SD=Standard Deviation; SE=Standard Error; CI=Confidence Interval

Intent to Treat Population using last observation carried forward method; All patients who received study medication and had a post-baseline body weight. Thirty-four percent (34%) of patients in Belviq and 38% in placebo dropped out before the 52-week endpoint.

[1]Least squares means adjusted for baseline value, baseline HbA1c stratum and prior antihyperglycemic medication stratum.

**p<0.001 compared to placebo. Type 1 error was controlled across the three endpoints.

Effect of BELVIQ on Cardiometabolic Parameters and Anthropometry in Patients with Type 2 Diabetes Mellitus

Patients in Study 3 were taking either metformin and/or a sulfonylurea at study start, and had inadequate glycemic control (HbA1c range 7-10%). Changes in HbA1c and fasting glucose with BELVIQ use are shown in Table 9.

Table 9. Mean Changes in Cardiometabolic Parameters and Waist Circumference in Patients with Type 2 Diabetes Mellitus

	BELVIQ N=256		Placebo N=252		BELVIQ minus Placebo (LSMean)
	Baseline	Change from Baseline (LSMean[1])	Baseline	Change from Baseline (LSMean)	
HbA1C (%)	8.1	-0.9	8.0	-0.4	-0.5*
Fasting glucose (mg/dL)	163.3	-27.4	160.0	-11.9	-15.5*
Systolic blood pressure (mmHg)	126.6	-0.8	126.5	-0.9	0.1
Diastolic blood pressure (mmHg)	77.9	-1.1	78.7	-0.7	-0.4
Heart Rate (bpm)	72.3	-2.0	72.7	-0.4	-1.6
	Baseline	% Change from Baseline (LSMean)	Baseline	% Change from Baseline (LSMean)	BELVIQ minus Placebo (LSMean)
Total Cholesterol (mg/dL)	173.5	-0.7	172.0	-0.1	-0.5
LDL Cholesterol (mg/dL)	95.0	4.2	94.6	5.0	-0.8
HDL Cholesterol (mg/dL)	45.3	5.2	45.7	1.6	3.6
Triglycerides (mg/dL)	172.1	-10.7	163.5	-4.8	-5.9
Waist Circumference (cm)	115.8	-5.5	113.5	-3.3	-2.2

Intent to Treat Population using last observation carried forward method; All patients who received study medication and had a post-baseline measurement.

* Statistically significant versus placebo based on the pre-specified gatekeeping method for controlling Type I error in key secondary endpoints.

[1]Least squares means adjusted for baseline value, baseline HbA1c stratum and prior antihyperglycemic medication stratum.

16 HOW SUPPLIED/STORAGE AND HANDLING

BELVIQ 10-mg tablets are supplied as blue-colored, round, biconvex, film-coated tablets debossed with “A” on one side and “10” on the other side and are available as follows:

- NDC 62856-529-10 Bottle of 100
- NDC 62856-529-51 Blister pack of 10

Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- BELVIQ is indicated for chronic weight management only in conjunction with a reduced-calorie diet and increased physical activity.
- Patients should be instructed to discontinue use of BELVIQ if they have not achieved 5% weight loss by 12 weeks of treatment.
- Patients should be informed of the possibility of serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions with the combined use of BELVIQ with other serotonergic drugs, including selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), triptans, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors

[MAOIs]), dietary supplements such as St. John's Wort and tryptophan, tramadol, or antipsychotics or other dopamine antagonists.

- Patients who develop signs or symptoms of valvular heart disease, including dyspnea or dependent edema should seek medical attention.
- Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BELVIQ therapy does not affect them adversely.
- Patients should be instructed to seek medical attention in the event of emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- Patients should be cautioned not to increase their dose of BELVIQ.
- Men who have an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.
- Patients should be instructed to avoid pregnancy or breastfeeding while undergoing BELVIQ therapy and to talk to their prescribing physician should they get pregnant or decide to breastfeed.
- Patients should tell their healthcare provider about all the medications, nutritional supplements and vitamins (including any weight loss products) that they may take while taking BELVIQ.

Manufactured by Arena Pharmaceuticals GmbH, Untere Brühlstrasse 4, CH-4800, Zofingen, Switzerland
Distributed by Eisai Inc., Woodcliff Lake, NJ 07677

PATIENT INFORMATION

BELVIQ® (BEL-VEEK)

(lorcaserin hydrochloride)

tablets

Read the Patient Information that comes with BELVIQ before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about BELVIQ, talk to your doctor or pharmacist.

What is BELVIQ?

BELVIQ is a prescription medicine that may help some obese adults or overweight adults who also have weight related medical problems lose weight and keep the weight off.

BELVIQ should be used with a reduced calorie diet and increased physical activity.

It is not known if BELVIQ is safe and effective when taken with other prescription, over-the-counter, or herbal weight loss products.

It is not known if BELVIQ changes your risk of heart problems or stroke or of death due to heart problems or stroke.

It is not known if BELVIQ is safe when taken with some other medicines that treat depression, migraines, mental problems, or the common cold (serotonergic or antidopaminergic agents).

It is not known if BELVIQ is safe and effective in children under 18 years old.

Who should not take BELVIQ?

Do not take BELVIQ if you:

- are pregnant or planning to become pregnant. BELVIQ may harm your unborn baby.

What should I tell my healthcare provider before taking BELVIQ?

Before you take BELVIQ, tell your doctor if you:

- **have or have had heart problems including:**
  - **congestive heart failure**
  - **heart valve problems**
  - **slow heart beat or heart block**
- have diabetes
- have a condition such as sickle cell anemia, multiple myeloma, or leukemia
- have a deformed penis, Peyronie's disease, or ever had an erection that lasted more than 4 hours
- have kidney problems

- have liver problems
- are pregnant or plan to become pregnant.
- are breast feeding or plan to breastfeed. It is not known if BELVIQ passes into your breastmilk. You and your doctor should decide if you will take BELVIQ or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

BELVIQ may affect the way other medicines work, and other medicines may affect how BELVIQ works.

Especially tell your doctor if you take medicines for depression, migraines or other medical conditions such as:

- triptans, used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, selective serotonin uptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), or antipsychotics
- cabergoline
- linezolid, an antibiotic
- tramadol
- dextromethorphan, an over-the-counter medicine used to treat the common cold or cough
- Rver-the-counter supplements such as tryptophan or St. John's Wort
- medicines to treat erectile dysfunction

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know all the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take BELVIQ?

- Take BELVIQ exactly as your doctor tells you to take it.
- Your doctor will tell you how much BELVIQ to take and when to take it.
  - Take 1 tablet 2 times each day.
  - **Do not** increase your dose of BELVIQ.
  - BELVIQ can be taken with or without food.
- Your doctor should start you on a diet and exercise program when you start taking BELVIQ. Stay on this program while you are taking BELVIQ.
- Your doctor should tell you to stop taking BELVIQ if you do not lose a certain amount of weight within the first 12 weeks of treatment.
- If you take too much BELVIQ or overdose, call your doctor or go to the nearest emergency room right away.

What should I avoid while taking BELVIQ?

- **Do not** drive a car or operate heavy machinery until you know how BELVIQ affects you. BELVIQ can slow your thinking.

What are the possible side effects of BELVIQ?

BELVIQ may cause serious side effects, including:

- **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions.**

  BELVIQ and certain medicines for depression, migraine, the common cold, or other medical problems may affect each other causing serious or life-threatening side effects. Call your doctor right away if you start to have any of the following symptoms while taking BELVIQ:

  - mental changes such as agitation, hallucinations, confusion, or other changes in mental status
  - coordination problems, uncontrolled muscle spasms, or muscle twitching (overactive reflexes)
  - restlessness
  - racing or fast heart beat, high or low blood pressure
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - muscle rigidity (stiff muscles)

- **Valvular heart disease.** Some people taking medicines like BELVIQ have had problems with the valves in their heart. Call your doctor right away if you have any of the following symptoms while taking BELVIQ:
  - trouble breathing
  - swelling of the arms, legs, ankles, or feet
  - dizziness, fatigue, or weakness that will not go away
  - fast or irregular heartbeat

- **Changes in your attention or memory.**

- **Mental problems.** Taking BELVIQ in high doses may cause psychiatric problems such as:
  - hallucinations
  - feeling high or in a very good mood (euphoria)
  - feelings of standing next to yourself or out of your body (disassociation)

- **Depression or thoughts of suicide.** You should pay attention to any mental changes, especially sudden changes, in your mood, behaviors, thoughts, or feelings. Call your healthcare provider right away if you have any mental changes that are new, worse, or worry you.
- **Low blood sugar (hypoglycemia) in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus.** Weight loss can cause low blood sugar in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus (such as insulin or sulfonylureas). You should check your blood sugar before you start taking BELVIQ and while you take BELVIQ.

- **Painful erections (priapism).** The medicine in BELVIQ can cause painful erections that last more than 6 hours. If you have an erection lasting more than 4 hours whether it is painful or not, stop using BELVIQ and call your doctor or go to the nearest emergency room right away.

- **Slow heart beat.** BELVIQ may cause your heart to beat slower. Tell your doctor if you have a history of your heart beating slow or heart block.
- **Decreases in your blood cell count.** BELVIQ may cause your red and white blood cell count to decrease. Your doctor may do tests to check your blood cell count while you are taking BELVIQ.

- **Increase in prolactin.** The medicine in BELVIQ may increase the amount of a certain hormone your body makes called prolactin. Tell your doctor if your breasts begin to make milk or a milky discharge or if you are a male and your breasts begin to increase in size.

The most common side effects of BELVIQ include:

- headache
- dizziness
- fatigue
- nausea
- dry mouth
- constipation
- cough
- low blood sugar (hypoglycemia) in patients with diabetes
- back pain

Tell to your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BELVIQ. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store BELVIQ?

Store BELVIQ at room temperature between 59°F to 86°F (15°C to 30°C).

Safely throw away medicine that is out of date or no longer need.

Keep BELVIQ and all medicines out of the reach of children.

General information about the safe and effective use of BELVIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BELVIQ for a condition for which it was not prescribed. Do not give BELVIQ to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about BELVIQ. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about BELVIQ that is written for health professionals.

For more information, go to www.BELVIQ.com Website or call 1-888-274-2378.

What are the ingredients in BELVIQ?

Active Ingredient: lorcaserin hydrochloride

Inactive Ingredients: silicified microcrystalline cellulose; hydroxypropyl cellulose NF; croscarmellose sodium NF; colloidal silicon dioxide NF; polyvinyl alcohol USP; polyethylene glycol NF; titanium dioxide USP; talc USP; FD&C Blue #2 aluminum lake; and magnesium stearate NF.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Rx Only

BELVIQ® is a registered trademark of Arena Pharmaceuticals GmbH, Zofingen, Switzerland
Manufactured by Arena Pharmaceuticals GmbH, Untere Brühlstrasse 4, CH-4800, Zofingen, Switzerland
Distributed by Eisai Inc., Woodcliff Lake, NJ 07677

FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market

Potential risk of cancer outweighs the benefits

This is an update to the FDA Drug Safety Communication: Safety clinical trial shows possible increased risk of cancer with weight-loss medicine Belviq, Belviq XR (lorcaserin) (/drugs/drug-safety-and-availability/safety-clinical-trial-shows-possible-increased-risk-cancer-weight-loss-medicine-belviq-belviq-xr) issued on January 14, 2020.

2-13-2020 FDA Drug Safety Communication

What safety concern is FDA announcing?

The U.S. Food and Drug Administration (FDA) has requested that the manufacturer of Belviq, Belviq XR (lorcaserin) voluntarily withdraw the weight-loss drug from the U.S. market because a safety clinical trial shows an increased occurrence of cancer. The drug manufacturer, Eisai Inc,. has submitted a request to voluntarily withdraw the drug.

What is FDA doing?

We are taking this action because we believe that the risks of lorcaserin outweigh its benefits based on our completed review of results from a randomized clinical trial assessing safety.

In January 2020 (/drugs/drug-safety-and-availability/safety-clinical-trial-shows-possible-increased-risk-cancer-weight-loss-medicine-belviq-belviq-xr), we announced we were reviewing clinical trial data and alerted the public about a possible risk of cancer associated with lorcaserin based on preliminary analysis of the data.

What should patients do?

Patients should stop taking lorcaserin and talk to your health care professionals about alternative weight-loss medicines and weight management programs. It’s best to dispose (/drugs/disposal-unused-medicines-what-you-should-know/drug-disposal-dispose-non-flush-list-medicine-trash) of unused lorcaserin using a drug take back location

(/drugs/disposal-unused-medicines-what-you-should-know/drug-disposal-drug-take-back-locations), but if you can't get to one you can dispose of lorcaserin in your household trash:

1. Mix the pills with an unappealing substance such as dirt, cat litter, or used coffee grounds; do not crush them.
2. Place the mixture in a container such as a sealed plastic bag.
3. Throw away the container in your trash at home.
4. Remove or delete all personal information on the prescription label of empty medicine bottles or packaging, then throw away or recycle them.

FDA is not recommending special screening for patients who have taken lorcaserin. Talk to your health care professional if you have questions.

What should health care professionals do?

Health care professionals should stop prescribing and dispensing lorcaserin to patients. Contact patients currently taking lorcaserin, inform them of the increased occurrence of cancer seen in the clinical trial, and ask them to stop taking the medicine. Discuss alternative weight-loss medicines or strategies with your patients.

FDA is not recommending special screening for patients who have taken lorcaserin. As with any individual patient, regardless of prior lorcaserin treatment, standard screening recommendations for cancer (https://www.cancer.gov/about-cancer/screening/screening-tests) should be implemented.

What did FDA find?

When FDA approved lorcaserin in 2012, we required the drug manufacturer to conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the risk of cardiovascular problems, which found that more patients taking lorcaserin (n=462; 7.7 percent) were diagnosed with cancer compared to those taking a placebo, which is an inactive treatment (n=423; 7.1 percent). The trial was conducted in 12,000 patients over 5 years. A range of cancer types was reported, with several different types of cancers occurring more frequently in the lorcaserin group, including pancreatic, colorectal, and lung.

How do I report side effects from lorcaserin?

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving lorcaserin or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Data Summary

We reviewed data from the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) clinical trial. It was a randomized, double-blind, placebo-controlled, multicenter, parallel group trial conducted between January 2014 and June 2018 in the U.S., Canada, Mexico, the Bahamas, Europe, South America, Australia, and New Zealand. The study population consisted of 12,000 men and women who were overweight or obese. Patients were required to have either established cardiovascular disease, or to be at least 50 years old for men or 55 years for women with type 2 diabetes mellitus plus at least one additional cardiovascular risk factor. Eligible patients were assigned randomly to either lorcaserin 10 mg twice daily or placebo. Approximately 96 percent of patients completed the study, and 62 percent who completed remained on treatment at the end of study. The median follow-up time was 3 years and 3 months.

The primary safety analysis showed no meaningful difference between lorcaserin and placebo in the risk of major adverse cardiovascular events, demonstrating noninferiority. The one-sided upper bound of the 95% confidence interval (CI) of the hazard ratio (HR) was less than 1.4 (the noninferiority margin). The HR (95% CI) was 1.005 (0.842, 1.198) for lorcaserin versus placebo.

There was a numerical imbalance in the number of patients with malignancies, with one additional cancer observed per 470 patients treated for one year. During the course of the trial, 462 (7.7 percent) patients treated with lorcaserin were diagnosed with 520 primary cancers compared to the placebo group, in which 423 (7.1 percent) patients were diagnosed with 470 cancers. Imbalances in specific cancers including pancreatic, colorectal, and lung contributed to the observed overall imbalance in cancer cases. There was no apparent difference in the incidence of cancer over the initial months of treatment, but the imbalance increased with longer duration on lorcaserin.

Drug Safety Communication (/media/135189/download) (PDF - 62KB)

Related Information

- National Cancer Institute: Cancer Screening Tests (https://www.cancer.gov/about-cancer/screening/screening-tests)
- Medline Plus: Obesity (https://medlineplus.gov/obesity.html)
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective (/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective)
- Think It Through: Managing the Benefits and Risks of Medicines (/drugs/drug-information-consumers/think-it-through-managing-benefits-and-risks-medicines)

Contact FDA

For More Info
855-543-DRUG (3784) and press 4
druginfo@fda.hhs.gov (mailto:druginfo@fda.hhs.gov)

Report a Serious Problem to MedWatch
Complete and submit the report Online (https://www.accessdata.fda.gov/scripts/medwatch/). Download form (/about-fda/medwatch-consumer-voluntary-reporting-pdf) or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

Weight-loss drug Belviq recalled

POSTED APRIL 09, 2020, 10:30 AM

Florencia Halperin, MD
Contributor

In February, the manufacturer of the weight-loss medication lorcaserin (Belviq, Belviq XR) voluntarily withdrew the drug from the US market at the request of the FDA. This was a result of emerging data showing that people who had taken the drug as part of a large clinical trial had an increased occurrence of cancer . ve years later.

What were the . ndings about Belviq, and why did this information come to light now?

Lorcaserin was approved by the FDA in 2012. As part of the approval process, the FDA reviewed a series of clinical trials that looked at its effects on weight and its safety profile, compared to a placebo.

Based on these studies, the drug was approved, but a larger study to assess its cardiovascular safety was mandated by the FDA. In that subsequent study, published in the *New England Journal of Medicine*, 12,000 people with overweight or obesity and cardiovascular disease (CVD) or risk factors for CVD took either lorcaserin or a placebo. During the three-year follow-up, as published in 2018, those who took lorcaserin had more weight loss and comparable rates of cardiovascular events compared to those who took a placebo. So from a cardiovascular safety perspective, the study was reassuring.

But the study subjects continued to be followed, and what recently came to light is that at five years, the group that took the drug has had a slight increase in the occurrence of cancers compared to those who took a placebo (7.7% of lorcaserin subjects developed cancer, compared to 7.1% in the placebo group). Increases in several different types of cancers were observed, including pancreatic, colorectal, and lung.

Where does the recall leave people who are currently taking Belviq?

Based on the evidence we have now, it is still uncertain whether lorcaserin truly increases the risk of cancer. And we don't know anything about the mechanisms of how this drug could have such effects. It is also critical to reiterate that this possible increase in cancer occurrence is very small; 7.1% of people developed cancer if they were taking placebo, and 7.7% if they were taking lorcaserin.

That said, people taking lorcaserin are advised to stop taking it and contact the doctor who prescribed it for guidance on next steps. The FDA is not recommending any special cancer screening or other testing at this time.

Could my doctor prescribe a di. erent weight-loss medication?

Loracaserin is one of several medications currently FDA-approved for weight loss in people who have overweight with weight-related medical issues, or who have obesity. For those who have not had success losing weight through diet, exercise, and other healthy lifestyle changes, or for people who have been unable to sustain the weight loss they do achieve, weight-loss medications can play an important role. By changing the biology of the systems that regulate weight, and suppressing appetite and cravings, medications can help people lose weight even if other strategies have not worked. Lorcaserin, for example, works by affecting brain serotonin signaling, making you feel more full, so you eat less.

However, since each medication works in a unique way, someone who experienced weight loss with lorcaserin is not necessarily going to experience a similar effect from another medication. You may need to work with your doctor to try different options to find one that is effective.

Do the new findings mean all weight-loss medications are unsafe?

These new . ndings do not in any way re. ect the safety of other weight-loss medications on the market. Weight-loss medications have a storied history with safety recalls, and lorcaserin is not the first weight-loss medication to get pulled off the market after many years of patient use — fenfluramine/phentermine (Fen-Phen) and sibutrimine (Meridia) are other examples.

Still, it is unsettling to learn that a widely used, FDA-approved medication demonstrates serious safety concerns. On the other hand, it is important to underscore that, as in the case of lorcaserin, the FDA evaluates safety outcomes, and continues to rigorously monitor products on the market. This is in contrast to weight-loss supplements, which are not regulated by the FDA. Americans spend millions of dollars every year on these unregulated weight-loss products, which tout incredible results with no credible studies and no ongoing safety monitoring, and which can have serious adverse health consequences.

Anyone considering weight-loss medications or products should work with licensed health care professionals. The experience with lorcaserin is a good reminder to use only interventions that have scientific studies that evaluate safety as well as benefits. And it is comforting that close monitoring and regulatory processes are in place to ensure our safety.

Related Information: Lose Weight and Keep It Off

Print

Related Posts:

Popular heartburn drug ranitidine recalled: What you…

10 behaviors for healthy weight loss

Behavioral weight loss programs are effective — but…

Benefits of a healthy diet — with or without weight loss

New FDA-approved weight loss device shows promise

COMMENTS	TOPICS
0	Diet and Weight Loss | Drugs and Supplements

Commenting has been closed for this post.

Footnote 9

Step 3: Clinical Research

While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body. "Clinical research" refers to studies, or trials, that are done in people. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins.

On this page you will find information on:

- Designing Clinical Trials
- Clinical Research Phase Studies
- The Investigational New Drug Process
- Asking for FDA Assistance
- FDA IND Review Team
- Approval

Designing Clinical Trials

Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol, that is developed by the researcher or manufacturer. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:

- Who qualifies to participate (selection criteria)
- How many people will be part of the study
- How long the study will last
- Whether there will be a control group and other ways to limit research bias
- How the drug will be given to patients and at what dosage
- What assessments will be conducted, when, and what data will be collected
- How the data will be reviewed and analyzed

Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies.

During Phase 1 studies, researchers test a new drug in normal volunteers (healthy people). In most cases, 20 to 80 healthy volunteers or people with the disease/condition participate in Phase 1. However, if a new drug is intended for use in cancer patients, researchers conduct Phase 1 studies in patients with that type of cancer.

Phase 1 studies are closely monitored and gather information about how a drug interacts with the human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what its acute side effects are.

As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies.

Approximately 70% of drugs move to the next phase

Phase 2

Study Participants: Up to several hundred people with the disease/condition.

Length of Study: Several months to 2 years

Purpose: Efficacy and side effects

In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed. Typically involving a few hundred patients, these studies aren't large enough to show whether the drug will be beneficial.

Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.

Approximately 33% of drugs move to the next phase

Phase 3

Study Participants: 300 to 3,000 volunteers who have the disease or condition

Length of Study: 1 to 4 years

Purpose: Efficacy and monitoring of adverse reactions

Researchers design Phase 3 studies to demonstrate whether or not a product offers a treatment benefit to a specific population. Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants.

Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects

Approximately 25-30% of drugs move to the next phase

Phase 4

Study Participants: Several thousand volunteers who have the disease/condition

Purpose: Safety and efficacy

Phase 4 trials are carried out once the drug or device has been approved by FDA during the Post-Market Safety Monitoring

Learn more about Clinical Trials (/clinical-trials-what-patients-need-know).

The Investigational New Drug Process

Drug developers, or sponsors, must submit an Investigational New Drug (IND) application to FDA before beginning clinical research.

In the IND application, developers must include:

- Animal study data and toxicity (side effects that cause great harm) data
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator

Asking for FDA Assistance

Drug developers are free to ask for help from FDA at any point in the drug development process, including:

- Pre-IND application, to review FDA guidance documents and get answers to questions that may help enhance their research
- After Phase 2, to obtain guidance on the design of large Phase 3 studies
- Any time during the process, to obtain an assessment of the IND application

Even though FDA offers extensive technical assistance, drug developers are not required to take FDA's suggestions. As long as clinical trials are thoughtfully designed, reflect what developers know about a product, safeguard participants, and otherwise meet Federal standards, FDA allows wide latitude in clinical trial design.

FDA IND Review Team

The review team consists of a group of specialists in different scientific fields. Each member has different responsibilities.

- ***Project Manager:*** Coordinates the team's activities throughout the review process, and is the primary contact for the sponsor.
- ***Medical Officer:*** Reviews all clinical study information and data before, during, and after the trial is complete.
- ***Statistician:*** Interprets clinical trial designs and data, and works closely with the medical officer to evaluate protocols and safety and efficacy data.
- ***Pharmacologist:*** Reviews preclinical studies.
- ***Pharmakineticist:*** Focuses on the drug's absorption, distribution, metabolism, and excretion processes.Interprets blood-level data at different time intervals from clinical trials, as a way to assess drug dosages and administration schedules.
- ***Chemist:*** Evaluates a drug's chemical compounds. Analyzes how a drug was made and its stability, quality control, continuity, the presence of impurities, etc.
- ***Microbiologist:*** Reviews the data submitted, if the product is an antimicrobial product, to assess response across different classes of microbes.

Approval

The FDA review team has 30 days to review the original IND submission. The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials. FDA responds to IND applications in one of two ways:

- Approval to begin clinical trials.
- Clinical hold to delay or stop the investigation. FDA can place a clinical hold for specific reasons, including:
    - Participants are exposed to unreasonable or significant risk.
    - Investigators are not qualified.
    - Materials for the volunteer participants are misleading.
    - The IND application does not include enough information about the trial's risks.

A clinical hold is rare; instead, FDA often provides comments intended to improve the quality of a clinical trial. In most cases, if FDA is satisfied that the trial meets Federal standards, the applicant is allowed to proceed with the proposed study.

The developer is responsible for informing the review team about new protocols, as well as serious side effects seen during the trial. This information ensures that the team can monitor the trials carefully for signs of any problems. After the trial ends, researchers must submit study reports.

This process continues until the developer decides to end clinical trials or files a marketing application. Before filing a marketing application, a developer must have adequate data from two large, controlled clinical trials.

What are the Clinical Trial Phases?

Watch this video to learn about the three phases of clinical trials.

Clinical Research Phase Studies

Phase 1

Study Participants: 20 to 100 healthy volunteers or people with the disease/condition.

Length of Study: Several months

Purpose: Safety and dosage

Footnote 10

U.S. FOOD & DRUG ADMINISTRATION

22 CASE STUDIES WHERE PHASE 2 AND PHASE 3 TRIALS HAD DIVERGENT RESULTS

January 2017

Table of Contents

22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results

I. Overview

Pre-market clinical testing usually progresses in phases, with increasingly rigorous methods at each phase. Product candidates that appear insufficiently safe or effective at one phase may not proceed to the next phase. Roughly 9 in 10 drugs/biologics that are tested in humans are never submitted to FDA for approval.[1] Typically, a candidate drug is submitted to the FDA for marketing approval after phase 3 testing. In recent years, there has been growing interest in exploring alternatives to requiring phase 3 testing before product approval, such as relying on different types of data and unvalidated surrogate endpoints.

To better understand the nature of the evidence obtained from many phase 2 trials and the contributions of phase 3 trials, we identified, based on publicly available information, 22 case studies of drugs, vaccines and medical devices since 1999 in which promising phase 2 clinical trial results were not confirmed in phase 3 clinical testing.[*] Phase 3 studies did not confirm phase 2 findings of effectiveness in 14 cases, safety in 1 case, and both safety and effectiveness in 7 cases. These unexpected results could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent.

This paper is not intended to assess why each of these unexpected results occurred or why further product development was not pursued. Rather, these cases, chosen from a large pool of similar examples, illustrate the ways in which controlled trials of appropriate size and duration contribute to the scientific understanding of medical products.

II. Clinical Trials: Understanding Medical Product Testing

In the classical drug development paradigm, pre-market clinical trials for drugs are conducted in three phases. The trials at each phase have a different purpose and help scientists answer different questions.

- *Phase 1 Trials*. In phase 1, researchers test the potential product in humans for the first time, to identify rudimentary product characteristics, such as how the body metabolizes a drug and how long it stays in the body, and to provide evidence that the product is not too toxic for further human testing. The treatment group is small (typically 20 – 80 healthy volunteers), but allows researchers to begin to evaluate the treatment's safety, adjust dosing schemes, and start to identify side effects. This information guides the design of phase 2 studies.

- *Phase 2 Trials*. Phase 2 studies are intended to explore the effectiveness of the product for a particular indication over a range of doses, and to assess short-term side effects. These studies typically involve a few hundred patients who have the target condition, but do not generally have other diseases that might obscure the effect of the drug on the target condition. Phase 2 trials may be randomized and/or controlled, but often measure laboratory values or other biomarkers rather than clinical outcomes (i.e., effects on how a patient feels, functions, or survives). When a phase

[*] For the purposes of this analysis, the terms "trial" and "study" are used interchangeably.

2 study does assess clinical outcomes, it is usually for relatively short periods of time and in a relatively small number of people. Sponsors assess phase 2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study.

- *Phase 3 Trials*. Compared to phase 2 trials, the goal of phase 3 trials is to test the experimental product in larger groups of people (typically 300 – 3000), in people who are more similar to those likely to use the product once marketed, and for longer periods of time. Phase 3 studies generally assess clinical outcomes, and are designed to determine whether the demonstrated benefits of the product outweigh its risks.

As discussed in Section III, below, the appropriate size and duration of clinical trials varies significantly from condition to condition, and product to product.[†]

For most approved drug products, clinical evaluation may be continued even after a product is on the market. These studies are termed phase 4 trials, and can be helpful to uncover information on new uses that can be shared with health care providers to refine prescribing advice or can indicate that new warnings should be added to the product's label.

III. Flexibility in Clinical Trial Design

In practice, clinical testing progression and design has become increasingly flexible as the science of clinical trials has evolved. Phase 1 might be combined with phase 2 if the drug is expected to have toxicity unacceptable for healthy volunteers. If the product's mechanism of action and safety profile are well characterized, phase 2 testing may be shortened or skipped altogether. When there is sufficient evidence that a change in a biomarker reliably predicts a clinical benefit, the biomarker can serve as a surrogate measure for that clinical benefit in a trial, and the effect of the product on the surrogate measure can be a basis for product approval. Surrogate measures are often biomarkers that help diagnose or monitor a disease, such as blood pressure to predict stroke risk or the amount of human immunodeficiency virus in the blood to predict the development of acquired immunodeficiency syndrome.

The nature of definitive trials also varies. Larger and longer trials may be needed if, for example, the condition to be treated is chronic or if the event the drug is intended to prevent occurs infrequently. Smaller or shorter trials may be needed where, for example, the drug produces a dramatic improvement in patients, or is intended for short-term conditions like many infections. Other factors, such as whether the condition is widespread or rare, whether it is life-threatening, and whether there are other effective treatments for the condition are also important in determining what kind of clinical testing is appropriate.

Where a drug or biologic is intended to treat a serious condition for which there are limited available alternative therapies, FDA has implemented four separate expedited development and review programs.[2] For example, when there is evidence that a biomarker is "reasonably likely to predict"

[†] Medical device testing often does not follow this "phase 1 - 3" paradigm or use the same "phase 1 – 3" vocabulary. In some cases, practical limitations related to the device or disease condition may limit the feasibility of a large randomized, controlled trial design. But the need, in certain circumstances, for one or more large well controlled studies to determine whether a device actually improves clinical outcomes can be equally applicable. Such trials serve a purpose similar to phase 3 drug and biologic trials. For editorial convenience, we use the phrase "phase 3" throughout the document to refer to both phase 3 drug and biologics trials, as well as "pivotal" and similar trials for devices.

clinical benefit, that biomarker can be a basis for approval under FDA's accelerated approval authority. In these situations, sponsors have been required to conduct post-market confirmatory studies to further define the clinical benefit of the drug.

While clinical testing progression and design has become increasingly flexible, and advances in biomedical science and statistics have enabled introduction of non-traditional study designs and data sources into phase 3 testing, a randomized, controlled, clinical trial (RCT) of a size and duration that reflect the product and target condition remains the gold standard for determining whether there is an acceptable benefit/risk profile for drugs and biologics. For more discussion on clinical trial design, including the unique features of RCTs that make such trials more likely to be definitive, see Appendix A.

IV. Case Studies

The methods underlying case selection, as well as a discussion of the limitations of this study, are described in Appendix B.

A. Phase 3 Trials Demonstrating Lack of Efficacy in a Promising Experimental Therapy

1. Bitopertin

Product	Bitopertin
Sponsor	Roche
Purpose	Add-on treatment of schizophrenia
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite statistically significant results in reducing the symptoms of schizophrenia in phase 2, in phase 3 trials Bitopertin failed to improve the negative symptoms of schizophrenia.

Schizophrenia is a chronic brain disorder in which people abnormally interpret reality and features three symptom categories: positive, negative and cognitive. Positive symptoms include hallucinations and delusions, while negative symptoms may include social withdrawal, lack of motivation, and reduced emotional reactivity. Cognitive symptoms include problems with memory and concentration.

Schizophrenia typically requires lifelong treatment with antipsychotic medications, which come in two types: typical and atypical. Both types block the brain's dopamine pathway, but atypical antipsychotics are less likely to cause certain undesired side effects (e.g., movement problems), making them useful for long-term management of patients with schizophrenia. However, atypical antipsychotics are still associated with undesirable side effects such as weight gain, increased cholesterol, and movement disruption.

Like dopamine, glycine is a neurotransmitter that has been implicated in the schizophrenia disease process. Over the past years, researchers have noted that people with schizophrenia have a decreased level of glycine in their blood and cerebrospinal fluid.[3] Bitopertin increases the availability of glycine in the synapse (the connection between nerve cells), suggesting a novel approach in the treatment of schizophrenia. A placebo-controlled, double-blind, eight week study randomized over 320 patients across 66 sites worldwide. The study found a statistically significant 25% reduction in negative symptoms among those patients who received the drug compared to those who received placebo.[4]

Three subsequent double-blind, placebo-controlled phase 3 studies evaluated the efficacy and safety of bitopertin when added to conventional drugs in patients with negative symptoms of schizophrenia. These studies together followed over 1800 patients for one year or more, and measured improvement in a patient's negative symptoms compared to symptoms before treatment began. However, results from two of these phase 3 studies found no evidence of a statistically significant improvement in negative symptoms over baseline in patients who received bitopertin add-on therapy compared to those who received placebo.[5, 6]

2. Brivanib

Product	Brivanib
Sponsor	Bristol-Myers Squibb
Purpose	Treatment of hepatocellular cancer
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising anti-tumor activity in phase 2 trials, in phase 3 trials Brivanib failed to improve overall survival of patients compared to approved treatment, and demonstrated identified unexpected toxicities.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, occurring in four out of five cancers that start in the liver.[7] Treatment options for liver cancer, depending on the stage and severity of cirrhosis, include surgery to remove the tumor, embolization to block blood supply to the tumor, radiation, and transplantation.[8, 9]

The only FDA-approved drug is sorafenib, which delays tumor growth and improves survival by inhibiting certain signals used in cell growth or function.[10, 11] Generally, sorafenib is administered to patients who are not candidates for local-directed therapies. To treat those patients who do not respond to sorafenib or who have severe side effects related to the drug, brivanib was developed. Brivanib inhibits a novel growth factor, in addition to those growth factors targeted by sorafenib.

A phase 2 trial was conducted in which 55 patients with advanced HCC received a daily dose of brivanib in the first-line setting.[12] According to the published report, using computed tomography (CT)/magnetic resonance imaging (MRI) measurements of tumor volume, one patient had a complete response, three had a partial response, and 24 had stable disease following exposure to brivanib. A second cohort of 46 patients received brivanib after failing sorafenib therapy or discontinuing sorafenib due to intolerable side effects.[13] Using the same CT/MRI tumor measurement criteria, according to the published report, two patients had a partial response and 19 had stable disease following treatment. Together the studies showed that brivanib showed antitumor activity, with almost half of participants being classified as having stable disease following treatment. The investigators also reported a manageable safety profile for patients with advanced HCC.

Several phase 3 RCTs designed to isolate the effects of brivanib, confirmed statistically significant antitumor activity, but found no evidence that treatment with brivanib improves the overall survival of patients with HCC. One phase 3 study, designed to compare brivanib to sorafenib, randomized over 1,100 patients with advanced HCC who had no prior drug treatment to receive either brivanib or sorafenib.[14] The median overall survival was 9.5 months in the brivanib group and 9.9 months in the sorafenib group, and the primary objective (i.e., non-inferiority of survival) of the study was not met. The authors concluded that brivanib was "less well-tolerated" than sorafenib, as patients receiving brivanib had significantly higher rates of decreased appetite, fatigue, hypertension, nausea, and low blood sodium levels. The authors also stated that patients who received brivanib had a more pronounced decline in physical function and in role function.

Another phase 3 study randomized 395 patients with advanced HCC in patients who previously received sorafenib to receive either brivanib or placebo.[15] This study did not demonstrate a statistically significant improvement in overall survival in patients who received brivanib as compared to placebo.

A third phase 3 study investigated whether brivanib could increase survival compared to placebo in Asian patients with advanced hepatocellular carcinoma who failed prior treatment with sorafenib; however, this study was discontinued by its sponsors and no results are available.[16]

A fourth phase 3 study compared brivanib as an additional treatment to chemoembolization with those receiving only chemoembolization in patients with HCC.[17] However, this trial was terminated early after the two other phase 3 studies mentioned above failed to show improvement in overall survival of patients with HCC. At termination, this study showed that brivanib had not improved overall survival (26.4 vs. 26.1 months).

3. Capsaicin Topical Patch (Qutenza) ‡

Product	Capsaicin topical patch (Qutenza)
Sponsor	NeurogesX
Purpose	Treatment of HIV-associated nerve pain
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of shingles-associated nerve pain.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite demonstrated efficacy in a related condition and positive clinical results in a proof of concept study, in an RCT pain control was similar in the Qutenza and control groups.

Many HIV patients experience a burning-type of pain, often in the feet or hands, as a result of nerve damage. Called HIV-associated distal symmetric polyneuropathy (HIV-DSP), it is the most common nerve complication of HIV infection, affecting over 50% of patients.[18-20]

Qutenza is made from capsaicin, the pungent component that makes chili peppers hot. Capsaicin acts on certain pain receptors in the skin by desensitizing nerve endings, resulting in analgesia and pain relief. In 2009, FDA approved Qutenza (8% patch) as a medicated skin patch for pain relief in patients with post-herpetic neuralgia, a painful complication following shingles.[21]

Researchers also studied the efficacy of capsaicin in a related intended use, painful HIV-DSP. An open-label pilot study assessed the efficacy and safety of NGX-4010 (capsaicin 8% patch) in twelve patients with HSV-DSP.[22] Following a single 60-minute NGX-4010 application, these patients were followed up for 12 weeks. The majority of these patients reported a significant reduction in pain, prompting the researchers to proceed to a large, controlled clinical trial.

In two similarly designed RCTs, 800 patients with HIV-DSP were randomized to receive NGX-4010 or a 0.04% concentration control patch. This low concentration control patch was considered too weak to actually treat HIV-DSP, but strong enough to cause the localized skin reactions that are common with capsaicin so that patients would not know to which group they had been assigned. While the initial study found significant pain relief with NGX-4010 over 12 weeks of treatment compared to controls, these findings were not replicated in the second study.[22, 23]

In 2012, a FDA Advisory Committee analyzed the two controlled trials and agreed that there was no substantial evidence of effectiveness for Qutenza in treating HIV-DSP.[24] The Advisory Committee did not recommend the approval of Qutenza, and FDA did not approve the drug.[25]

‡ Product names in parentheses are brand names.

4. Darapladib

Product	Darapladib
Sponsor	GlaxoSmithKline
Purpose	Add-on to a statin for prevention of cardiovascular disease complications in patients with prior heart attack
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite exciting biomarker evidence in phase 2, in phase 3 trials darapladib failed to reduce the risk of heart attack or cardiac death compared with placebo in patients with chronic cardio vascular disease.

Cholesterol builds up in blood vessels of patients with cardiovascular disease, hardening the arteries in an inflammatory process called atherosclerosis.[26] Atherosclerosis restricts blood flow to the heart muscle, causing heart attacks.

Atherosclerosis is thought to be driven by inflammation. Lp-PLA2 is a protein produced by inflammatory cells, and blood levels of Lp-PLA2 are thought to predict heart attack risk.[27] A phase 2 study found both impressively reduced blood levels of Lp-PLA2 and stabilized atherosclerotic plaques in patients administered darapladib in addition to a statin (a cholesterol-reducing medication), compared to placebo plus a statin.[28] Another phase 2 study indicated that darapladib significantly reduced interleukin-6, another cardiovascular inflammatory marker.[29] Mechanistically, then, darapladib seemed promising. Human Genome Science CEO Tom Watkins predicted that darapladib was a "blockbuster in the making."[30]

The phase 3 STABILITY trial randomized over 15,000 patients with chronic, stable heart disease to take darapladib and a statin or a placebo and a statin, and monitored their cardiovascular outcomes over a median of 3.7 years.[31] The STABILITY trial's primary outcome measures were cardiovascular death, heart attack, and hospitalization for acute cardiac events. An additional phase 3 trial, the SOLID-TIMI 52 trial, randomized over 13,000 patients to receive either darapladib or a placebo within 30 days of a heart attack and followed their cardiovascular outcomes over a median of 2.5 years.[32] The study's primary outcome measures were cardiovascular death, nonfatal heart attack, and nonfatal stroke.

Neither study demonstrated benefit. Primary outcome event rates were 10.4% on placebo and 9.7% on darapladib in STABILITY, a difference that was not statistically significant. Primary outcome event rates in SOLID-TIMI 52 were 15.6% on placebo and 16.3% on darapladib, a lean in the opposite direction that was also not statistically significant.[33]

5. Dexmecamylamine

Product	Dexmecamylamine
Sponsor	Targacept/AstraZeneca
Purpose	Add-on treatment of depression
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite statistically significant results on measures of depression in phase 2, in the phase 3 trial dexmecamylamine proved no more effective than a placebo as add-on treatment for depression.

First-line therapies for depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These drugs increase the amount of serotonin and norepinephrine in the brain − neurotransmitters known to have a role in mood.[34]

Researchers have also hypothesized that drugs that activate certain other receptors called nicotinic neural receptors, such as the drug dexmecamylamine, could normalize the activity in these receptors and potentially be a treatment for depression.[35] In 2009, a phase 2 trial randomized 270 participants on SSRIs to receive either dexmecamylamine or placebo over a course of eight weeks. The study found that those who took dexmecamylamine improved more on a standard depression scale compared to placebo.[36]

With these promising phase 2 results, dexmecamylamine underwent four phase 3 studies in which a total of 614 study participants whose depression did not improve with standard SSRI or SNRI therapies were randomized to receive dexmecamylamine or placebo while continuing their SSRI or SNRI therapy. After eight weeks of add-on treatment, these studies found no difference between the treatment effects of dexmecamylamine and placebo in treating depression on standard depression scales in any of the phase 3 studies.[37-39]

6. Exhale Drug-Eluting Stent

Product	Exhale Drug-Eluting Stent
Sponsor	Broncus Technologies
Purpose	Reduction of shortness of breath in patients with emphysema
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent result in phase 3 trial	Despite statistically significant results on measures of lung function and symptoms in phase 2, in the phase 3 trial the Exhale Stent failed to improve lung function or symptoms in patients with emphysema.

Emphysema is a disease in which air sacs in the lungs called alveoli are gradually destroyed. Alveoli inflate and deflate with breathing, allowing inhaled oxygen to enter the blood and carbon dioxide to be exhaled. In emphysema, the alveoli hyperinflate and eventually rupture, trapping air in the lungs. As a result, fresh, oxygen-rich air cannot enter the lungs properly, causing progressive shortness of breath. It is frequently caused by many years of smoking and has no cure. Treatment for emphysema is intended to relieve symptoms, prevent complications, and slow disease progression. Therapies may involve smoking cessation, oxygen supplementation, medications such as bronchodilators (drugs that widen airway passages), surgery to reduce lung volume, and lung transplantation.[40]

A new bronchoscopic procedure was designed to reduce hyperinflation and improve airflow in emphysema. Called airway bypass, the procedure involves insertion of a flexible tube called a bronchoscope through the mouth so that the airways can be visualized. Once a diseased site is identified, a needle pierces the airway wall to create a new passage so that trapped air can escape.[41] A device smaller than a pencil eraser called the Exhale Drug-Eluting Stent is then placed in the newly created passageway to keep it open. A drug is included in the stent to prevent tissue growth in the new passage. A phase 2 study assessed the effects of the Exhale stents in 35 patients with severe emphysema by measuring how well their lungs took in and released air and whether their symptoms improved.[42] At the 6-month follow-up, there were statistically significant improvements in symptoms and various indices of lung function, as compared to baseline, leading researchers to conclude that the stents reduce hyperinflation and provide clinical improvement.

A phase 3 study further investigated whether these Exhale airway stents could improve lung function and reduce breathlessness in severely affected emphysema patients.[43] More than 300 patients were randomized to undergo either the airway bypass with Exhale stent placement or a sham procedure (a fake procedure in which bronchoscopes were used, but no airway walls were pierced and no stents were placed).[44] At 6 months, there were no differences in lung volume or shortness of breath between the two groups. The study thus concluded that Exhale airway stents provide no sustained benefit in patients with emphysema.

7. Experimental HSV-2 Vaccine

Product	Experimental HSV-2 Vaccine
Sponsor	Chiron (now Novartis Vaccines & Diagnostics)
Purpose	Prevention of genital herpes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite positive biomarker results in phase 2, in the phase 3 trials the vaccine did not prevent genital herpes.

Genital herpes is a common sexually transmitted disease caused by herpes simplex virus type 1 (HSV-1) or the generally more serious type 2 (HSV-2). Most people with herpes have no symptoms, but others may have painful genital sores that tend to recur. People with weakened immune systems, including individuals with HIV/AIDS, organ transplants, and cancer, are at increased risk for severe herpes infections. Pregnant women can also pass the infection to newborns, causing neonatal herpes, a rare but potentially life-threatening disease.[45] There is no cure for herpes, but there are medicines to prevent recurrences or shorten the duration of those recurrences.

An HSV-2 vaccine was developed by Chiron. Two phase 2 studies randomized over a hundred persons with no antibodies to HSV-2 in their blood to receive one of three different doses of the vaccine. The studies showed that the vaccine induced an antibody response similar to persons who had a naturally-acquired HSV-2 infection.[46]

Two phase 3 RCTs followed, involving almost 2,400 persons with no detectable antibodies for HSV-2 who were followed for one year after their final immunization.[47] These studies, however, showed that despite producing an antibody response similar to natural HSV-2 infection, vaccine recipients acquired HSV-2 infection at a rate similar to placebo (4.6% of placebo group versus 4.2% of vaccine group). Researchers concluded that the vaccine produced only a partial and transient protection against HSV-2 infection.[48]

8. Glutamic Acid Decarboxylase Vaccine

Product	Glutamic Acid Decarboxylase (GAD) Vaccine
Sponsor	Diamyd Medical
Purpose	Preservation of insulin secretion for patients with recent-onset type 1 diabetes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising biomarker results in phase 2, in the phase 3 study treatment with GAD vaccine did not improve pancreatic function or clinical outcomes.

Type 1 diabetes is an autoimmune disease in which a person's pancreas stops producing insulin. It affects adults and children and occurs when the body's immune system attacks and destroys the insulin-producing cells in the pancreas, called beta-cells. While intensive insulin therapy can delay the onset and slow progression of kidney failure, blindness, and nerve damage, these complications continue to cause high rates of morbidity and mortality.[49]

Vaccination with Glutamic Acid Decarboxylase (GAD) to control the abnormal immune response was proposed as a strategy to prevent or delay loss of beta-cell function. Although intensive insulin therapy improves glycemic control and is the therapeutic gold standard, insulin itself does not treat the underlying disease process. Treatment with therapies that down-regulate other parts of the immune system, including specific antibodies targeting important mediators of the immune response, have been tried but to date have not proved effective and have caused serious adverse reactions.[50]

In a phase 2 study, 70 patients recruited within 18 months of their type 1 diabetes diagnosis were randomly assigned to receive injections of GAD or placebo.[51] The primary endpoint was the change from baseline to month 15 in C-peptide levels, a measure of beta-cell function that drops as beta cell function declines. The C-peptide levels gradually decreased in both study groups, but patients receiving GAD injections showed significantly less decline in C-peptide levels than the patients receiving a placebo injection. This suggested that vaccination with GAD could potentially preserve the insulin-producing function of beta cells. The researchers claimed that the results provided a preliminary proof of concept.

In the phase 3 trial, 334 patients were randomly assigned to one of three study treatments and followed for 15 months: four doses of GAD, two doses of GAD followed by two doses of placebo, or four doses of placebo. The same time points from the phase 2 trial were used to measure C-peptide levels and other clinical outcomes such as insulin requirement, plasma glucose, glycosylated hemoglobin levels and rate of hypoglycemia.[52] The primary outcome was the change in C-peptide levels between the baseline visit and the 15-month visit. The phase 3 trial did not confirm the preliminary results and concluded that treatment with GAD did not significantly reduce the loss of C-peptide or improve any important clinical outcomes over a 15-month period.

9. Imiquimod (Aldara 5% Cream)

Product	Imiquimod (Aldara 5% Cream)
Sponsor	3M
Purpose	Treatment of molluscum contagiosum (MC) lesions in children
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of external anogenital warts.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite demonstrated efficacy in another viral skin infection and promising phase 2 results on clearance of MC lesions, in the phase 3 trial treatment with imiquimod cream was no more likely to clear MC lesions than treatment with placebo.

Molluscum contagiosum (MC) is a relatively common viral skin infection that primarily affects children. It is characterized by clusters of pearly, flesh-colored, dome-shaped bumps on the skin surface. These lesions are usually painless, but may be itchy and inflamed. If scratched, the lesions can spread to other areas of the body or to other persons, and can become infected with bacteria. MC disappears spontaneously, typically after 6 to 12 months, but some bumps can last up to four years.[53]

Common treatments for MC include cryotherapy (freezing with liquid nitrogen), curettage (scraping), topical agents, and lasers.[54] These treatment modalities can be effective but uncomfortable, especially for children. There are no FDA-approved drug treatments for MC.[55]

Imiquimod is a topical drug that is FDA-approved to treat external genital and perianal warts, which are caused by a different skin virus.[56] The drug works by stimulating the immune system's reaction to the virus, thereby strengthening the body's ability to fight off the infection. Researchers hypothesized that because imiquimod was effective for one viral skin infection, it might also be effective for others, leading researchers to investigate imiquimod's efficacy in MC.

A randomized, single blinded phase 2 clinical trial compared weekly cryotherapy to daily topical imiquimod in 74 children over 16 weeks. This study suggested impressive drug efficacy, with over 90% of those receiving imiquimod experiencing complete clearance of MC lesions at 12 weeks.[57] In the cryotherapy group, all lesions were cleared.[57] However, pain, blistering, and scarring were significantly more common in the cryotherapy group, making imiquimod look promising as a better tolerated, effective treatment for MC.[57]

Imiquimod cream was then evaluated in two double-blind phase 3 RCTs involving a total of 702 pediatric MC patients aged 2-12.[58] These children received imiquimod cream or placebo cream three times per week for up to 16 weeks and were assessed at week 18 for complete clearance of MC lesions. In the first study, the complete clearance rate was 24% in the imiquimod group compared with 26% in the vehicle group. In the second study, the clearance rate was 24% in the imiquimod group compared with 28% in the vehicle group. These studies thus failed to demonstrate any efficacy against MC. In addition, children who received imiquimod were more likely to experience application site reactions, conjunctivitis, low white blood cell counts, and inflamed lymph nodes.[58]

10. Iniparib

Product	Iniparib
Sponsor	Sanofi
Purpose	Add-on treatment of "triple negative" breast cancers
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising phase 2 results on both tumor response and survival, in the phase 3 trial adding iniparib to an established chemotherapy regimen did not improve survival.

Breast cancer is the most common cancer in women.[59] Triple-negative breast cancer is a subtype of breast cancer that is aggressive and difficult to treat. It is called triple-negative because the cancer cells do not over-express three different receptors; the cancer could otherwise be treated by chemotherapies and/or agents targeted to the receptors.

Iniparib showed strong activity in preclinical testing, enhancing the effects of standard chemotherapy on triple-negative metastatic breast cancer cells.[60, 61] In phase 2 testing, 123 patients with metastatic triple-negative breast cancer were randomized to receive either standard chemotherapy or standard chemotherapy plus iniparib. Adding iniparib to a standard chemotherapy regimen significantly improved tumor response and overall survival, without increasing toxicity.[62]

Despite promising phase 2 results, iniparib was not shown to be effective in phase 3 testing. Five hundred nineteen patients with metastatic triple-negative breast cancer were randomly assigned to receive either standard chemotherapy regimen or the standard regimen plus iniparib. The phase 3 trial did not identify any significant safety concerns, but the addition of iniparib to the standard regimen did not demonstrate any improvement in overall or progression-free survival.[63] Overall survival of the patients receiving standard chemotherapy was 11.1 months, versus 11.8 months for those also receiving iniparib.[63]

11. Lithium

Product	Lithium
Sponsor	King's College London (UK)
Purpose	Add-on treatment to delay disease progression of amyotrophic lateral sclerosis
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of bipolar disorder.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite positive effects on disease progression and survival in a phase 2 trial, in the phase 3 trial treatment with lithium did not improve survival, health status or quality of life.

Amyotrophic lateral sclerosis (ALS), sometimes called Lou Gehrig's disease (after the famous baseball player who was diagnosed with it), is a nervous system disease that causes muscle weakness. In ALS, the nerve cells that control the movement of muscles gradually die, leading to progressive weakness. Affected patients gradually lose ability to move their arms and legs, speak, eat, and breathe. Most ALS patients die within 2 to 5 years of diagnosis.[64]

Most cases of ALS have an unknown cause, but scientists believe that there is a genetic mutation in up to 10% of cases.[64-66] There is no cure for ALS, and riluzole is the only FDA-approved drug for the treatment of ALS.[67, 68] This drug extends patient survival by two to three months.[67, 69],

A proof of concept study randomized 44 ALS patients to receive daily doses of either riluzole or riluzole plus lithium.[70] Over a 15-month period, the study compared the survival rate and disease progression between the two groups. For disease progression, the study measured muscle strength and lung function (volume of air expired after a full inspiration) every three months. At the end of the study, all patients treated with lithium and riluzole were alive while 30% of patients who received riluzole alone had died. The study also showed that patients who received lithium had a slower disease progression compared to those who did not. The researchers thus concluded that lithium delays ALS progression.

A phase 3 placebo-controlled study followed and randomized over 200 ALS patients.[71] This study evaluated the safety and efficacy of lithium combined with riluzole, compared to placebo combined with riluzole. Over an 18-month period, the study compared (1) the overall survival of patients, and (2) health outcomes such as mobility, self-care, usual activities, pain or discomfort, anxiety, and depression. At the end of the study, the number of patients alive was similar between the treatment groups (50% in the lithium group versus 59% in the placebo group).[72] As for health outcomes, there was a marked deterioration in functional health status and quality of life in patients assigned to both groups with no difference between groups in their rates of decline. The study thus concluded that, while there was no safety concern, lithium has no evidence of benefit in patients with ALS.

12. MAGE-A3 vaccine

Product	MAGE-A3 vaccine
Sponsor	GlaxoSmithKline
Purpose	Treatment of patients with non-small cell lung cancer (NSCLC) following surgery
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite a promising proof of concept trial of this targeted immune therapy, in the phase 3 trial the MAGE-A3 vaccine conferred no clinical benefit when compared to a placebo.

Broadly, lung cancer comes in two forms: small cell and NSCLC. Current therapies for treatment of NSCLC include surgical removal of the cancer, chemotherapy, and radiation therapy, yet long-term survival rates remain low.[73]

Recent advances in cancer research indicate the potential for treating NSCLC by harnessing the body's immune system. Certain tumor cells exhibit surface molecules (antigens) that can be targeted by therapeutic cancer vaccines, potentially preserving healthy cells.[74] One example of these cell surface antigens is MAGE-A3, a tumor-specific antigen present on the surface of certain tumor cells. Approximately 33% of NSCLCs express MAGE-A3, which is not seen in normal lung cells, thus making it a potential target for NSCLC therapies.

A phase 2 study evaluated a MAGE-A3 vaccine as a treatment for patients with MAGE-A3-positive NSCLC. Following surgery to remove as much of the tumor as possible, 182 patients were randomized to receive either the MAGE-A3 vaccine or placebo 13 times over 27 months. The results showed a non-statistically significant improvement in disease-free survival and overall survival among patients receiving this cancer vaccine.[75] The study was only large enough only to provide proof of concept. The sponsor determined that the results were promising enough to propel the vaccine to the largest phase 3 trial of a NSCLC therapy ever undertaken.[76]

In the phase 3 MAGRIT trial, investigators randomized 2,272 patients with completely resected MAGE-A3-positive NSCLC to receive 13 intramuscular injections of either the vaccine or placebo using the same schedule as the phase 2 trial.[77] The study, however, did not demonstrate that treatment with MAGE-A3 cancer vaccine increased patients' disease-free survival (60.5 months vs. 57.9 months, a statistically non-significant difference).[77] The results of the study led the researchers to conclude that this cancer vaccine offers no clinical benefit in patients with NSCLC.[77]

13. NicVAX Vaccine

Product	NicVAX vaccine
Sponsor	Nabi Biopharmaceuticals
Purpose	Smoking cessation
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results of phase 3 trial	Despite phase 2 evidence suggesting positive biomarker and clinical results, in the phase 3 trials the abstinence rate in the NicVAX group was similar to that in the placebo group.

Nicotine is the primary addictive agent in tobacco. Nicotine vaccines aim to stimulate the immune system to produce nicotine-specific antibodies, which would bind with the nicotine in the bloodstream and prevent or slow the rate at which the nicotine reaches the brain.[78] This, in turn, might reduce the urge to smoke, leading to cessation.

One phase 1/2 and four phase 2 trials of one such vaccine, NicVAX, were conducted by Nabi Biopharmaceuticals.[79] All of these trials, which enrolled between 11 and 301 patients, focused on the safety and immunogenicity of NicVAX, and identifying the best dosing regimen. The phase 2b placebo-controlled trial with 301 patients also assessed efficacy of NicVAX for smoking cessation in smokers who wanted to quit.[80] In this study, those smokers who developed the highest concentrations of anti-nicotine antibodies in response to the vaccine were significantly more likely to maintain abstinence for 8 weeks than smokers receiving placebo. Collectively, these trials identified a 6-injection, high-dose regimen as the most likely to be effective, based on the anti-nicotine antibodies measured.[81]

Two phase 3 RCTs were conducted in which about 2,000 patients were given 6 vaccinations of NicVAX or placebo.[81] The last vaccination was at week 26, and the primary endpoint was the number of patients who remained abstinent for 16 weeks. This timeframe corresponded to the peak anti-nicotine antibody levels observed in the phase 2 trials. Despite the suggestions of efficacy in the phase 2b trial, one of phase 3 trials reported similar abstinence rates of approximately 11% in the NicVAX and placebo groups, failing to demonstrate efficacy.[81] The other phase 3 trial also failed to demonstrate efficacy.[§][81]

[§] Data for the second phase 3 trial were not reported in the paper.

14. Velimogene Aliplasmid (Allovectin-7)

Product	Velimogene Aliplasmid (Allovectin-7)
Sponsor	Vical
Purpose	Treatment of metastatic melanoma
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite evidence of tumor shrinkage in phase 2, in the phase 3 trial Allovectin-7 reduced tumor size in significantly fewer patients than two marketed therapies in late-stage melanoma patients.

A largely curable disease if detected early and surgically removed, melanoma is relatively resistant to treatment and generally deadly in its advanced stages. Melanoma has been shown to respond to therapies that stimulate the immune system to recognize and target melanoma cells.

In early phase 1 studies in advanced melanoma patients, one such therapy−Allovectin-7, a gene transfer therapy directly injected into melanoma tumors–was able to shrink tumors, including those distant from injected tumors.[82] Additional apparent evidence of effectiveness was generated in subsequent studies, most notably in an uncontrolled phase 2 study revealing complete or partial tumor shrinkage in 11.8% of late-stage melanoma patients who had previously failed on or could not tolerate conventional chemotherapy who were injected with Allovectin-7. Tissue examinations from two patients revealed no evidence of melanoma.[83] Based on the results of this study, the drug advanced to a phase 3 multinational clinical trial.

That trial featured 390 patients with stage III and IV melanoma who were randomly assigned to receive Allovectin-7 or one of two marketed therapies used to treat advanced melanoma.[84] Allovectin-7 failed to meet its endpoints. Allovectin-7 proved significantly less effective than these therapies, registering a favorable tumor response rate in 4.6% of patients receiving it for at least 24 months compared to 12.3% of patients on the other treatments.

B. Phase 3 Trials Demonstrating Lack of Safety in a Promising Experimental Therapy

15. Olanzapine Pamoate (Zyprexa Relprevv)

Product	Olanzapine Pamoate (Zyprexa Relprevv)
Sponsor	Eli Lilly
Purpose	Long-acting injection treatment for schizophrenia
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, in oral short-acting formulation for treatment of schizophrenia
Problem identified in phase 3 trial	Lack of safety
Divergent result in phase 3 trials	Although a different formulation of this drug was already approved, the phase 3 studies identified a serious safety risk of the long-acting formulation, requiring safety monitoring.

Schizophrenia is a chronic brain disorder characterized by an altered perception of reality. Symptoms may include hallucinations, delusions, and disordered thinking and behavior.[85, 86] Medication compliance in schizophrenia is a challenge, as roughly half of the patients with the disease have difficulty adhering to medical treatment.[87] A useful option is to inject patients with a long-acting formulation of the desired drug to ensure sustained treatment without the need for daily oral doses or daily injections.

Eli Lilly thus developed a long-acting, injectable formulation of its atypical antipsychotic olanzapine for use in patients with schizophrenia. Early phase studies showed evidence of non-inferiority to oral olanzapine, and did not identify new safety concerns.[88]

A subsequent phase 3 trial evaluated the efficacy of long-acting olanzapine injectable compared to placebo, and another phase 3 trial compared its efficacy with oral olanzapine. Both studies confirmed that the new long-acting formulation was effective in reducing the severity and frequency of schizophrenia symptoms.[88] However, early in these trials, two episodes of profound sedation occurred in the first hour after injection. These episodes triggered a review of all adverse events reported in trials of the injection formulation, as well as ongoing surveillance. Other incidents of sedation, dizziness, confusion and/or loss of consciousness in the immediate post-injection period were reported,** some occurring as late as three hours after injection.[88] This phenomenon became known as post-injection delirium sedation syndrome (PDSS).

In 2008, an FDA Advisory Committee reviewed the compiled evidence, which showed clear efficacy along with sometimes profound PDSS in 0.07% of injections and about 1.2% of patients.[89] The Advisory Committee determined that it would be worth trying to manage the risks of the injectable formulation in order to make the product available for patients with a history of non-adherence. It recommended approval, but with the imposition of a mandatory post-injection period of observation.[90] The FDA went on to approve the long-acting drug with a Risk Evaluation and Mitigation Strategy, which requires that all patients be observed by healthcare professionals for three hours after injection to ensure medical care is available if needed.[91]

** PDSS mimics olanzapine overdose, leading investigators to hypothesize that the injected olanzapine may have entered a blood vessel, leading to rapidly rising blood levels instead of the planned gradual release of the drug. Citrome L. Olanzapine pamoate: A stick in time. International Journal of Clinical Practice. 2009;63:140–50.

C. Phase 3 Trials Demonstrating Lack of Efficacy and Lack of Safety in a Promising Experimental Therapy

16. Aliskiren (Rasilez, Tekturna)

Product	Aliskiren (Rasilez, Tekturna)
Sponsor	Novartis
Purpose	Add-on treatment for prevention of congestive heart failure (CHF) complications
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of hypertension.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite approval of the drug for a related indication and positive biomarker effects in a proof of concept study, in the phase 3 trial adding aliskiren to standard therapy did not reduce cardiovascular-related death or CHF re-hospitalization after discharge, and increased the incidence of kidney failure and low blood pressure.

Congestive heart failure (CHF) occurs when the heart fails to pump enough blood to meet the needs of the body. When the heart fails to pump effectively, the amount of a hormone called renin rises in the bloodstream, causing fluid to build up in the body. Fluid overload can be quantified using a lab test called brain natriuretic peptide (BNP); an elevated BNP is associated with greater fluid overload and is indicative of a CHF exacerbation.[92]

It is well established that drugs that block the effects of renin can improve heart failure, but they also raise renin levels, thereby limiting the effectiveness of the medication. Pharmaceutical companies have developed drugs called direct renin inhibitors in hopes of improving treatment for CHF and high blood pressure. One such drug is aliskiren, which significantly reduced plasma BNP and renin activity compared to placebo in a proof of concept trial.[93]

Investigators evaluated aliskiren's clinical efficacy in the 2013 ASTRONAUT trial by randomizing over 1,600 patients hospitalized for CHF to take aliskiren or placebo for a year, in additional to standard therapy. The primary outcome measure was a composite including cardiovascular-related death or CHF-related rehospitalization. While BNP levels decreased, adding aliskiren to standard therapy did not reduce cardiovascular-related death or CHF rehospitalization after discharge compared to placebo: 10% of the patients receiving aliskiren and 11% of the patients receiving placebo died, indicating no significant mortality benefit to taking the drug. Moreover, patients receiving aliskiren had significantly higher rates of kidney failure and low blood pressure, as well as elevated potassium levels (not statistically significant), compared with patients who received placebo.[94]

17. CoStar Drug-Eluting Stent

Product	CoStar Drug-Eluting Stent
Sponsor	Conor Medsystems
Purpose	Reduction of heart attack risk in patients with coronary artery disease
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in phase 3 trial	Despite approval in the European Union and positive results in a small trial, in an RCT patients who received a CoStar stent had worse outcomes than those who received a different stent.

The heart's main blood supply comes from the coronary arteries. Coronary artery disease (CAD) results in a narrowing of these arteries, which restricts blood flow to the heart. Poor blood flow to the heart can lead to heart attacks and poor cardiac function. Coronary stents are wire-mesh tubes implanted in narrowed heart arteries to prop open the vessels, thereby preventing serious cardiac events. Drug-eluting stents are coated with a drug intended to augment the device's mechanical effects to help keep the artery open, and have gained popularity in recent years.

One such stent was the CoStar, which was coated with paclitaxel, an anti-cancer drug that inhibits scar formation around a stent, thus preventing re-narrowing of the artery. A small clinical study of the CoStar stent conducted outside the U.S. suggested that this stent performed as well as other marketed stents.[95] On this basis, the stent received European Union approval and was widely used in Europe.[96] Before approval in the U.S., however, the FDA insisted upon a large, double-blind, controlled study to demonstrate the CoStar stent's safety and comparability to available products.

Investigators conducted a clinical trial of 1,700 patients in the U.S. to support an application for FDA approval. The CoSTAR II trial was a RCT comparing the CoStar stent with the Boston Scientific Taxus Express2™ paclitaxel-eluting stent in the treatment of CAD. The primary outcome measure was major adverse cardiac events (MACE) at eight months, defined as a composite of target vessel re-narrowing, heart attack, and cardiac-related death. In the study, the CoStar stent showed a significantly higher MACE rate (11%) than the Taxus stent (6.9%).[97] Vessels in which the CoStar stent had been placed were significantly more likely to re-narrow (32%) than those in the comparison group (24%) and patients treated with the CoStar stent had a nearly 2-fold higher rate of needing a repeat coronary artery procedure to treat a recurrent blockage. The heart attack and stent thrombosis rates were numerically higher in patients treated with the CoStar stent, though the difference was not statistically significant.

18. Figitumumab

Product	Figitumumab
Sponsor	Pfizer
Purpose	Add-on treatment of advanced non-small cell lung cancer (NSCLC)
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in phase 3 trial	Despite positive clinical results in phase 2 for this targeted therapy, adding figitumumab to established chemotherapy regimens in phase 3 failed to improve survival, and in combination with one regimen increased serious adverse events and deaths.

Broadly, lung cancer comes in two forms: small cell and NSCLC. Current therapies for treatment of NSCLC include surgical removal of the cancer, chemotherapy, and radiation therapy, yet long-term survival rates remain low.[73]

Figitumumab was developed to inhibit a specific growth factor (IGF-1R) thought to contribute to the development and progression of NSCLC, among other cancers.[98, 99] In animal testing, it enhanced the anti-tumor effects of standard chemotherapies, and in phase 1 testing figitumumab appeared to inhibit the target pathway and showed signs of antitumor activity against several types of cancers, including NSCLC.[98] In a phase 2 study, NSCLC patients receiving figitumumab in combination with a standard chemotherapy regimen (carboplatin and paclitaxel) appeared to show a higher response rate than patients receiving carboplatin and paclitaxel alone.[98, 100]

Based on these results, two phase 3 trials were conducted comparing figitumumab plus various standard therapies to the standard therapies alone, in a total of 1264 patients with NSCLC.[101, 102] Both studies were halted early because figitumumab failed to improve overall survival. Further, combining figitumumab with one of these standard regimens showed a trend toward decreased overall survival and increased the incidence of treatment-related serious adverse events (SAEs) and deaths, with 21% of patients receiving figitumumab experiencing SAEs, compared with 12% of patients receiving the standard chemotherapy regimen alone.[102] The rate of treatment-related-death in patients receiving figitumumab was 5%, versus 1% in the standard regimen patients.[102]

After the phase 3 trials were terminated early for lack of efficacy and safety concerns, Pfizer retracted the article describing the phase 2 data.[103] The company discovered that tumor shrinkage had not been confirmed in all responding patients, deviating from Pfizer's standard operating procedures. The corrected data showed a lower response rate.

19. Recombinant Factor VIIa (NovoSeven)

Product	Recombinant Factor VIIa (NovoSeven)
Sponsor	Novo Nordisk
Purpose	Reduction of intracerebral bleeding and hematoma size in patients with stroke
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of hemophilia.
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 Trial	Despite positive clinical results in phase 2, in the phase 3 trials patients with intracerebral bleeding who received recombinant factor VIIa experienced no clinical benefits and an increased incidence of serious adverse events compared to patients who received placebo.

A stroke is a disruption of the brain's blood supply, leading to brain cell death. There are two kinds of stroke: ischemic and hemorrhagic. Ischemic stroke accounts for over 85% of all strokes, and occurs when blood flow to the brain is blocked by a blood clot. Hemorrhagic stroke is less common than ischemic stroke, and occurs when blood flow to the brain is disrupted by a bleed in the brain. Hemorrhagic stroke is often devastating because there is no effective treatment to stop the bleeding.

Factor VIIa is an essential protein in the body's clot-forming pathway. Recombinant factor VIIa (rFVIIa) is a product that has been used for a number of years to treat individuals with hemophilia who do not respond to conventional treatment. Researchers hypothesized that giving rFVIIa to patients experiencing an acute hemorrhagic stroke could reduce bleeding, and thus reduce the severity of bleeding and disability. In a placebo-controlled, double-blinded trial with 399 patients, researchers were heartened to find that treatment with rFVIIa within four hours after the onset of a hemorrhagic stroke reduced the amount of bleeding in the brain, reduced mortality, and improved patients' functional outcomes at 90 days.[104]

Subsequently, in order to further evaluate the efficacy of rFVIIa in improving survival and functional outcomes among patients, investigators randomized nearly 850 patients with acute hemorrhagic stroke to either placebo, 20 micrograms per kilogram rFVIIa, or 80 micrograms per kilogram of rFVIIa in the phase 3 FAST trial. The primary outcome measure was severe disability or death 90 days after the stroke. Although patients who received either dose of the study drug did have smaller bleeding volumes than those in the placebo group, they experienced no clinical benefit; approximately 20% of patients died no matter what they received, and rates of significant disability were comparable between the three groups.[105] Patients who received rFVIIa also experienced a statistically significant increase in thromboembolic events compared to those who received placebo.

20. Semagacestat

Product	Semagacestat
Sponsor	Eli Lilly
Purpose	Improvement of cognitive and functional status in persons with Alzheimer's Disease
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 Trial	Despite promising biomarker results in phase 2, the phase 3 trial was terminated early because patients who received semagacestat had worsened cognitive and functional status and an increased risk of skin cancer compared to patients who received placebo.

Alzheimer's Disease (AD) is chronic and progressive; survival after diagnosis can range from four to 20 years, depending on the individual and other coexisting health conditions.[106] Currently, there are several FDA-approved medications for the condition – three cholinesterase inhibitors (Aricept/donepezil, Exelon/rivastigmine, Razadyne/galantamine) and one N-methyl-D-aspartate receptor antagonist (Namenda/memantine) – but their efficacy is limited and they do not slow disease progression.

AD is associated with a buildup of amyloid-beta protein in the brain, and that protein is thought by many to play an important role in the disease process. Brain amyloid has been considered a biomarker with potential clinical meaning, and researchers have hypothesized that reducing amyloid-beta may improve disease symptoms. Semagacestat blocks gamma-secretase, an enzyme involved in the creation of amyloid-beta, and thus is intended to prevent the buildup of amyloid-beta in the brain; semagacestat was also expected to reduce blood concentrations of amyloid-beta protein.[107] A phase 2 trial that examined the effect of semagacestat in AD did show a reduction in blood levels of amyloid-beta among patients receiving the drug daily for 14 weeks.[108] Investigators were hopeful that semagacestat's effect on the levels of this [peptide] in blood would translate into clinically meaningful improvements in the disease.

A phase 3 trial randomized over 1,500 patients to receive placebo or semagacestat for 18 months.[109] The primary outcomes were the change in cognition from baseline to month 18 in the ADAS-cog and ADCS-ADL, which are measures of cognition and function, respectively. The trial was terminated before completion because patients taking semagacestat experienced worse cognitive and overall functioning over the course of the trial compared to those taking a placebo.[109] Treatment with semagacestat was associated with decreases in blood concentrations of amyloid-beta, but was also associated with a statistically significant dose-related decline in primary outcomes including activities of daily living, global functioning, cognitive functioning, and quality of life, compared to placebo. Patients taking semagacestat had more adverse events – including infections, skin cancers, and total cancers – compared to placebo. In fact, patients receiving semagacestat had at least double the risk of developing skin cancer compared to patients receiving placebo.

21. Torcetrapib

Product	Torcetrapib
Sponsor	Pfizer
Purpose	Prevention of cardiovascular events in patients with a history of cardiovascular disease or type 2 diabetes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results of phase 3 trial	Even though torcetrapib improved biomarker (cholesterol) levels in phase 2 testing, in the phase 3 trial it increased mortality and cardiac events compared with placebo in patients at high cardiovascular risk.

Having high cholesterol puts patients at risk of developing heart disease, the leading cause of death among Americans. Cholesterol is carried in the blood stream in different ways. HDL-cholesterol (HDL-C) is sometimes referred to as "good" cholesterol because higher levels of HDL-C are associated with a lower risk of cardiovascular disease; conversely, LDL-cholesterol (LDL-C) is sometimes referred to as "bad" cholesterol because higher levels of LDL-C are associated with an increased risk of adverse cardiovascular events.[110] Consequently, clinicians often aim to raise HDL-C and to reduce LDL-C in an attempt to reduce a patient's cardiovascular risk.

Cholesteryl ester transfer protein (CETP) is an enzyme that transfers cholesterol molecules from HDL to LDL. Torcetrapib blocks CETP, thereby simultaneously raising HDL-C and lowering LDL-C. The drug performed well on measures of LDL-C and HDL-C in phase 2 trials, although small increases in blood pressure were sometimes observed with torcetrapib treatment.[111, 112] Pfizer executive Jeff Kindler said that torcetrapib might be "one of the most important developments in our generation."[113] Pfizer reportedly spent over $800 million to develop and test torcetrapib.[114]

A phase 3 study randomized over 15,000 participants with coronary artery disease, history of stroke, diabetes, or peripheral artery disease to receive either torcetrapib or placebo in addition to a statin. The primary outcome measure was the time to first occurrence of a major cardiovascular disease event (e.g., heart attack, stroke); other outcomes measures included cholesterol levels and blood pressure. Although HDL-C increased and LDL-C decreased significantly among those receiving torcetrapib compared with those receiving placebo, the drug was not shown to be effective and proved to be dangerous. Patients who received torcetrapib were 25% more likely to suffer a major adverse cardiac event, and were 58% more likely to die from any cause, than those taking the placebo (both results were statistically significant).[115] The torcetrapib group also showed a significant increase in blood pressure.[115] The trial was halted three years earlier than expected because of these compelling and unexpected safety concerns.[113]

22. V710 vaccine

Product	V710 vaccine
Sponsor	Intercell (nowValneva) / Merck
Purpose	Vaccine to prevent Staphylococcus aureus infection
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 trial	Despite promising biomarker results in phase 2, a phase 3 study of V710 vaccine was terminated due to lack of efficacy and with potential risk for serious adverse events and death.

Staphylococcus aureus, called "staph" for short, is one of the most common bacteria found on the skin and nose of even healthy persons. It does not usually cause any harm other than skin infections like infected pimples and boils. However, staph can cause serious and life-threatening infections if it enters the bloodstream. Between 10% and 30% of patients with staph in their blood will die from this infection.[116] Staph infection can be prevented by good hygiene especially hand-washing, sterile wound dressings, and antibiotics prior to certain medical procedures. An effective staph vaccine has not been made.[117]

V710 is an investigational staph vaccine that elicited a good immune response in early studies.[118] A phase 2 study randomized 206 chronic hemodialysis patients (who are at high risk for staph) to receive either V710 or placebo on days 1, 28, and 180. The study results indicated that V710 produced an antibody response evident by day 28 and which was sustained for up to one year after initial vaccination.[119] There were no serious adverse effects attributed to the vaccine.

A phase 3 study followed, involving almost 8000 patients from 26 countries.[120] These patients, scheduled to have cardiothoracic surgery, were randomized to receive a single injection of either V710 or placebo. This study was designed to determine whether the vaccine could prevent staph infection in the blood and/or chest wound infection for up to 90 days following the surgery. However, this study was terminated early because of safety concerns and low efficacy. The study showed that V710 did not prevent staph infection any better than placebo (2.6 v. 3.2 infections per 100 person-years). There were also more cases of multi-organ failure and death among those who acquired staph infection in the V710 group compared to placebo. The researchers concluded that, in addition to the identified safety concerns, V710 was unlikely to yield a significant clinical benefit.[121]

V. Discussion

The following summarizes the wide range of circumstances in which phase 2 findings did not accurately predict safety and/or efficacy and provides some additional observations stemming from these case studies.

A. Large RCTs Can Produce Unexpected Results Across all Types of Products, Patients, and Conditions

These case studies demonstrate that large phase 3 RCTs can generate critical evidence across all types of products, patients, and diseases. Both safety and efficacy failures occurred even when the phase 2 studies were relatively large (e.g., recombinant VIIa), and even when the product was already approved for another condition (e.g., aliskiren). In some cases, the phase 3 study revealed that short-term results found in the phase 2 study were not associated with a long-term benefit (e.g., bitopertin) or that the product had toxicity that was not uncovered in the phase 2 study (e.g., semagacestat). Unexpected evidence from a phase 3 trial does not always result in non-approval -- in one case, the evidence led to the addition of a safety monitoring requirement (long-acting formulation of olanzapine pamoate). The Summary Table in Appendix C provides an overview of the type of unexpected results in the phase 3 studies presented here.

We identified unexpected results in phase 3 trials whether the underlying disease was acute (e.g., V710 vaccine) or chronic (e.g., Qutenza); common (e.g., CoStar drug-eluting stent) or rare (e.g., lithium); and preventative (e.g., HSV-2 vaccine) or intended to treat symptoms (e.g., dexmecamylamine). Similarly, unexpected results occurred whether the experimental product targeted early disease (e.g., GAD vaccine) or later stages (e.g., figitumumab), and whether the product targeted adults (e.g., darapladib) or children (imiquimod). There were unexpected failures in phase 3 trials whether the promise in phase 2 was a positive response on a potential surrogate endpoint (e.g., torcetrapib) or on clinical outcomes (e.g., iniparib). Unexpected failures in phase 3 occurred with all types of medical products – drugs, vaccines and other biologics, and devices.

In several cases where more limited data from phase 2 studies seemed to show a benefit, the more conclusive phase 3 evidence revealed that the experimental product actually increased the frequency of the problem it was intended to prevent. For example, torcetrapib, which was intended to reduce heart attacks by increasing “good” cholesterol (HDL) and lowering “bad” cholesterol (LDL), showed in phase 2 trials that the drug did in fact increase HDL and lower LDL. Yet, the phase 3 trial, which examined whether the drug actually reduced heart attacks, showed that patients taking the drug were actually 25% more likely to suffer a major cardiac event than those in the control group.

B. An Experimental Product’s Presumed Mechanism of Action Does Not Automatically Predict Clinical Effects

As these case studies show, a medical product’s apparent mechanism of action does not automatically predict clinical outcomes.[122] There was a plausible mechanism of action associated with most products in these case studies, but that often did not translate into clinical benefit. Down-regulating specific immune functions associated with diabetes did not delay progression of the disease (GAD vaccine). A vaccine targeting proteins present on certain tumor cells but not on normal lung cells was not effective against lung cancer (MAGE-A3 vaccine). A compound that inhibited growth factors associated with lung and other cancers (figitumumab) was not proven effective.

These cases also show that phase 2 data do not necessarily predict the product's safety and efficacy, even where the product is already approved for a related condition and phase 2 data seem promising for the second condition. In several of the cases reviewed here, the experimental product was already approved for one condition and seemed promising for a different but related condition, but full testing failed to show that the drug was effective and/or demonstrated that the drug was dangerous for the related condition. Imiquimod turned out to be effective against some skin viruses but not others. Qutenza proved effective against nerve pain associated with shingles, but not nerve pain associated with HIV. Recombinant Factor VIIa was shown to stimulate blood clotting in a way that helps those with hemophilia but not patients with hemorrhagic stroke. Safety failures occurred even where the phase 3 trial tested a new formulation of an already-approved product (olanzapine pamoate in a long-acting formulation to treat schizophrenia).

Many medical conditions are complex; targeting a single component of a condition cannot be presumed to have a positive effect on the patient unless there is objective clinical evidence. This array of unexpected results from phase 3 studies demonstrates the complexity of the interaction between a medical product and the patient, and how logical presumptions without corroborating clinical evidence can be unreliable.

C. Many Biomarkers Do Not Reliably Predict Clinical Outcomes[††]

While biomarkers have many important uses in clinical practice and product testing, most have not been shown to reliably predict clinical outcomes. As several of these case studies illustrate, promising biomarker data in phase 2 do not necessarily translate into effective product performance. Biomarker data were promising in phase 2 testing in products targeting conditions ranging from heart disease (aliskiren, darapladib, torcetrapib) to Staph infection (V710 vaccine), and from AD (semagacestat) to herpes infection (HSV-2 vaccine). These experimental products were not proven effective when tested in phase 3 trials.

VI. Conclusions

Rapid advances in biomedical sciences are now helping researchers improve the predictive capacity of phase 1 and phase 2 trials in certain circumstances. Improved molecular understanding of cancer, for instance, is already helping us design phase 1 and phase 2 trials that can demonstrate clinical benefits persuasively, by matching the patient to a specific experimental drug based on molecular mutations rather than tumor type.

At the same time, the 22 cases explored in this paper demonstrate that phase 2 results can inaccurately predict safety and/or effectiveness for medical products in a wide range of diseases and patient populations. These cases also help illustrate the potential public health implications of undue reliance on phase 2 studies and the benefits of conducting Phase III studies. As a result of the Phase III studies discussed in this paper, patients outside of clinical trials were not subjected to drugs that would not benefit them or to the risk of unnecessary serious toxicities, and did not suffer unnecessary financial expenditures. Where effective alternative therapies existed, they were not diverted from proven

[††] For a review of the array of uses of biomarkers, from use in disease monitoring to use as surrogates for clinical outcomes, see U.S. Food and Drug Administration-National Institutes of Health Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/ Co-published by National Institutes of Health (US), Bethesda (MD).

treatments; where an implanted medical device was at issue, patients were spared unnecessary surgical procedures.

Phase 3 trials help care providers understand when a medical product provides clinical benefit to patients that outweigh the risks. They also help researchers understand when a purported mechanism of action is credible and merits further development, allowing researchers to avoid investing substantial time and resources going in the wrong direction, resources that could be deployed to identify a truly effective product. As we continue to explore alternatives to requiring phase 3 testing, it is important to keep in mind the benefits they provide to both patients and to the medical research enterprise.

Appendix A: RCTs and Clinical Trial Design Considerations

In many cases, demonstration of an acceptable benefit/risk profile requires a randomized, controlled, clinical trial, of a size and duration that reflect the product and target condition. Since the 1940s, when the first RCTs were done, the practice of medicine has greatly benefited from the availability of the unbiased, evidence-based information they produce.[123] Three crucial elements of the RCT that make it more likely to be definitive are: comparing the product to a control; randomizing patients between the control and treatment groups; and, where possible and appropriate, blinding the patients and clinicians as to whether patients are receiving the product being studied or the control.

Control: The control group is a group of patients that is as close to the treated group as possible in all relevant characteristics, other than whether they receive the medical product being tested. The purpose of the control group is to ensure that any improvement in the treated group is above and beyond that resulting from the natural course of the disease, supportive medical care received as part of the trial, or a placebo effect. The control need not be a placebo; the experimental product may be tested against one or more known effective therapies.

Randomization: Randomizing patients between the control and treatment groups helps ensure that any difference observed between the treated and controlled groups is likely caused by the product being studied. It does so by ensuring that factors that might affect the outcome, such as age, gender, and other medical conditions, are approximately equally distributed between the treated and control groups.

Blinding: Blinding means not allowing various parties to the trial to know who has been assigned to the treated or control groups. Blinding is intended to reduce the possibility that unconscious bias, rather than the medical product, caused any difference between the treatment and control groups.

Together, these features of RCTs make it possible to separate the effects of the product being tested from other influences. Advances in biomedical science and statistics, however, can also enable a more flexible approach to determining which trial designs can be considered "adequate and well controlled." The agency has issued an array of draft and final guidances describing circumstances under which trial designs that do not follow the typical paradigms may provide reliable evidence, including:

Use of adaptive designs, potentially allowing changes in trial protocol based on interim trial results. This can allow enrollment of fewer patients and potentially shorter trial duration, but requires significant safeguards to avoid introduction of bias.[124]

Use of enrichment designs, potentially allowing highly targeted selection of trial patients. This can allow enrollment of fewer patients and those who are more likely to respond to the test product, but may present challenges with regard to the interpretability and generalizability of the trial results.[125]

Use of historical controls instead of a classically controlled trial, potentially allowing patients outside the trial to serve as the control. This may allow enrollment of fewer patients and allow all patients in the trial to receive the test product, but sacrifices randomization and blinding.[126] Historical control designs are usually reserved for circumstances where the natural history of the disease is very well characterized and relatively uniform.[127]

Appendix B: Methods

We present a set of 22 phase 3 RCTs published or otherwise publicly reported in sufficient detail since 1999, in which the study produced unexpected evidence despite phase 2 results suggesting that the product could be safe and effective. The intent of these case studies is to shed light on the kinds of medical insights Phase 3 trials can generate, and illustrate the ways that the results of phase 2 trials, alone, can be misleading. We selected examples from among numerous additional candidates, to represent as wide an array of conditions, types of patients, and types and formulations of prescription medical products as possible.

A. Sources

We identified candidate case studies through expert elicitation, and review of published scientific articles and the trade press.

- Expert elicitation. We engaged FDA medical product reviewers and scientists in the following Offices. These experts identified examples of phase 3 RCTs that had produced unexpected results, and provided insights into ways that the information from phase 3 trials is used, beyond the approval decision (see discussion in section VI).

    - Office of the Commissioner: Deputy Commissioner for Medical Products and Tobacco; Office of Pediatric Therapeutics; the Office of Orphan Products Development.
    - Center for Drug Evaluation and Research (CDER): the Deputy Center Director for Clinical Science
    - CDER, Office of New Drugs, Office of Drug Evaluation: the Division of Cardiovascular and Renal Products; the Office of Antimicrobial Products; the Office of Hematology and Oncology Products; the Division of Neurology Products; the Division of Psychiatry Products; the Division of Pediatric and Maternal Health; the Division of Metabolism and Endocrinology Products; and the Division of Anesthesia, Analgesia, and Addiction Products.
    - Center for Biologics Evaluation and Research: the Center Director, Deputy Director, and the Office of Cellular, Tissue, and Gene Therapy.
    - Center for Devices and Radiologic Health: the Deputy Center Director for Science.

- Review of published, peer-reviewed, literature. The scientific information on the phase 2 and 3 trials examined in these case studies was obtained from PubMed and ClinicalTrials.gov. The Centers for Disease Control and Prevention and National Institute of Health websites provided additional epidemiologic information.

- Trade press and other public/online sources. We reviewed trade press and annual compilations of pipeline failures published by FierceBioTech and Genengnews.com to identify candidates for review and possible analysis. While we relied primarily on peer-reviewed literature for the actual analyses, in a few cases, where the failed phase 3 trial was not published, we used company press releases where these were sufficiently detailed. For some case studies, an Advisory Committee transcript provided additional information on the phase 3 trial results.

B. Limitations

This is not an analysis of "success rates" or the predictive accuracy of phase 2 data broadly. A rigorous study involving all or a random sample of all medical products that enter phase 3 is not possible. Many phase 3 trials are never published and are otherwise not in the public domain; cases that could not be

presented using only public sources could not be included. Even FDA may be unaware of certain phase 3 trials, if they are conducted abroad and not under an Investigational New Drug Application.[‡‡] Reporting of results to Clinicaltrials.gov was not required by statute until 2008; further, during the time of this study, summary results were only required for approved, licensed, or cleared products. The bias toward publishing only successful trials has been well documented.[128] When product development is halted, the sponsor often releases only a press announcement, or makes no announcement at all, and the scientific issues behind the termination of product development are not available.[129]

Rather, we attempted to identify cases that could be illustrative across different types of products, conditions, and patients. Further, we focused on the medical information produced in phase 3 trials, not business or other non-scientific reasons for halting product development.

[‡‡] When a drug sponsor wants to test its potential drug in humans for the first time, the sponsor must submit an Investigational New Drug Application to the FDA providing, among other things, the preclinical data that shows that the drug is reasonably safe for initial testing in humans, and the sponsor's protocols for proposed clinical studies. The sponsor may proceed after 30 days, unless FDA objects.

Appendix C: Summary Table

Summary Table: An overview of the types of divergent results observed in the phase 3 studies

Product	Purpose	Lack of			Approved for Any Indication at Time of Phase 3 Trial	Page
		Efficacy	**Safety**	**Efficacy and Safety**		
Aliskiren (Rasilez, Tekturna)	Add-on treatment of prevention of congestive heart failure (CHF) complications	✓			✓	21
Bitopertin	Add-on treatment of schizophrenia	✓				5
Brivanib	Treatment of hepatocellular cancer	✓				6
Capsaicin Topical Patch (Qutenza)	Treatment of HIV-associated nerve pain	✓			✓	8
CoSTAR Drug-Eluting Stent	Reduction of heart attack risk in patients with coronary artery disease			✓		22
Darapladib	Prevention of cardiovascular disease complications in patients with prior heart attack	✓				9
Dexmecamylamine	Add-on treatment of depression	✓				10
Exhale Drug-Eluting Stent	Reduction of shortness of breath in patients with emphysema	✓				11
Experimental HSV-2 Vaccine	Prevention of genital herpes	✓				12
Figitumumab	Treatment of advanced non-small cell lung cancer			✓		23
Glutamic Acid Decarboxylase Vaccine	Preservation of insulin secretion in patients with recent-onset type 1 diabetes	✓				13
Imiquimod (Aldara)	Treatment of molluscum contagiosum lesions	✓			✓	14
Iniparib	Add-on treatment of “triple negative” breast cancers	✓				15
Lithium	Treatment to delay disease progression of amyotrophic lateral sclerosis	✓			✓	16
MAGE-A3 Vaccine	Treatment of patients with non-small cell lung cancer following surgery	✓				17
NicVAX Vaccine	Smoking cessation	✓				18
Olanzapine Pamoate (Zyprexa Relprevv)	Long-acting treatment for schizophrenia		✓		✓	20
Recombinant Factor VIIa (NovoSeven)	Reduction of intracerebral bleeding and hematoma size in patients with stroke			✓	✓	24

Semagacestat	Improvement of cognitive and functional status in Alzheimer's disease		✓	25
Torcetrapib	Prevention of cardiovascular disease events in patients with a history of cardiovascular disease or type 2 diabetes		✓	26
V710 Vaccine	Vaccine to prevent *Staphylococcus aureus* infection		✓	27
Velimogene Aliplasmid (Allovectin-7)	Treatment of metastatic melanoma	✓		19

References

1. DiMasi, J.A., H.G. Grabowski, and R.W. Hansen, *Briefing: Cost of Developing a New Drug (November 18, 2014) [Presentation]*. 2014, Tufts University. [Accessed: December 20th, 2016]; Available from: http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf.
2. US Food and Drug Administration *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*. 2014. [Accessed: December 22, 2016]; Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf
3. Heresco-Levy, U., et al., *Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia.* Arch Gen Psychiatry, 1999. **56**(1): p. 29-36.
4. Umbricht, D., et al., *Effect of bitopertin, a glycine reuptake inhibitor, on negative symptoms of schizophrenia: a randomized, double-blind, proof-of-concept study.* JAMA Psychiatry, 2014. **71**(6): p. 637-46.
5. Roche. *Roche provides update on the first two of six phase III studies of bitopertin in schizophrenia*. 2014. [Accessed: December 19, 2016]; Available from: http://www.roche.com/media/store/releases/med-cor-2014-01-21.htm.
6. Goff, D.C., *Bitopertin: the good news and bad news.* JAMA Psychiatry, 2014. **71**(6): p. 621-2.
7. American Cancer Society. *Liver Cancer*. 2016 [Accessed: December 21, 2016]; Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/003114-pdf.pdf.
8. Sandhu, D.S., et al., *Treatment options for hepatocellular carcinoma.* Expert Rev Gastroenterol Hepatol, 2008. **2**(1): p. 81-92.
9. PDQ® Adult Treatment Editorial Board, *PDQ Adult Primary Liver Cancer Treatment*, in *PDQ Cancer Information Summaries*. 2002, US National Cancer Institute: Bethesda (MD). Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032553/.
10. Bayer HealthCare Pharmaceuticals Inc. *Nexavar (sorafenib) Prescribing Information*. 2010. [Accessed: June 5, 2015]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021923s008s009lbl.pdf.
11. Zhu, A.X., et al., *SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma.* J Clin Oncol, 2015. **33**(6): p. 559-66.
12. Park, J.W., et al., *Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma.* Clin Cancer Res, 2011. **17**(7): p. 1973-83.
13. Finn, R.S., et al., *Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma.* Clin Cancer Res, 2012. **18**(7): p. 2090-8.
14. Johnson, P.J., et al., *Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study.* J Clin Oncol, 2013. **31**(28): p. 3517-24.
15. Llovet, J.M., et al., *Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study.* J Clin Oncol, 2013. **31**(28): p. 3509-16.
16. Bristol-Myers Squibb. *Comparison of Brivanib and Best Supportive Care (BSC) With Placebo and BSC for Treatment of Liver Cancer in Asian Patients Who Have Failed Sorafenib Treatment (BRISK-APS)*. 2015 [Accessed: December 19, 2016]; Available from: https://clinicaltrials.gov/ct2/show/NCT01108705.

17. Kudo, M., et al., *Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial.* Hepatology, 2014. **60**(5): p. 1697-707.
18. Morgello, S., et al., *HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy: the Manhattan HIV Brain Bank.* Arch Neurol, 2004. **61**(4): p. 546-51.
19. Simpson, D.M., et al., *HIV neuropathy natural history cohort study: assessment measures and risk factors.* Neurology, 2006. **66**(11): p. 1679-87.
20. Keltner, J.R., et al., *HIV-associated distal neuropathic pain is associated with smaller total cerebral cortical gray matter.* J Neurovirol, 2014. **20**(3): p. 209-18.
21. US Food and Drug Administration. *Summary Review - NDA 22395 (Qutenza)*. 2009. [Accessed: December 21, 2016]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022395s000sumr.pdf.
22. Simpson, D.M., et al., *An open-label pilot study of high-concentration capsaicin patch in painful HIV neuropathy.* J Pain Symptom Manage, 2008. **35**(3): p. 299-306.
23. Clifford, D.B., et al., *A randomized, double-blind, controlled study of NGX-4010, a capsaicin 8% dermal patch, for the treatment of painful HIV-associated distal sensory polyneuropathy.* J Acquir Immune Defic Syndr, 2012. **59**(2): p. 126-33.
24. US Food and Drug Administration. *Meeting Transcript: Anesthetic & Analgesic Drug Products - Advisory Committee (AADPAC) Meeting.* 2012. [Accessed: December 22, 2016]; Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM304332.pdf.
25. US Food and Drug Administration. *Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting.* 2012. [Accessed: December 22, 2016]; Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM304331.pdf.
26. Centers for Disease Control and Prevention. *Coronary Artery Disease (CAD)*. 2015 [Accessed: December 19, 2016]; Available from: https://www.cdc.gov/heartdisease/coronary_ad.htm.
27. Thompson, A., et al., *Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies.* Lancet, 2010. **375**(9725): p. 1536-44.
28. Serruys, P.W., et al., *Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque.* Circulation, 2008. **118**(11): p. 1172-82.
29. Mohler, E.R., 3rd, et al., *The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study.* J Am Coll Cardiol, 2008. **51**(17): p. 1632-41.
30. Berkrot, B. *Human Genome exploring options after rebuff of Glaxo*. Reuters, 2012. [Accessed: December 21, 2016]; Available from: http://www.reuters.com/article/us-humangenome-idUSBRE83N19620120424.
31. White, H.D., et al., *Darapladib for preventing ischemic events in stable coronary heart disease.* N Engl J Med, 2014. **370**(18): p. 1702-11.
32. O'Donoghue, M.L., et al., *Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial.* Jama, 2014. **312**(10): p. 1006-15.
33. Hassan, M., *STABILITY and SOLID-TIMI 52: Lipoprotein associated phospholipase A2 (Lp-PLA2) as a biomarker or risk factor for cardiovascular diseases.* Glob Cardiol Sci Pract, 2015. **2015**: p. 6.
34. Thase, M.E. and T. Denko, *Pharmacotherapy of mood disorders.* Annu Rev Clin Psychol, 2008. **4**: p. 53-91.

35. Lippiello, P.M., et al., *TC-5214 (S-(+)-mecamylamine): a neuronal nicotinic receptor modulator with antidepressant activity.* CNS Neurosci Ther, 2008. **14**(4): p. 266-77.
36. Dunbar G and Hosford D, *The potential of the nicotinic channel blocker TC-5214 as augmentation treatment in patients with major depression.* European Neuropsychopharmacology, 2010(20): p. S334-S.
37. AstraZeneca and Targacept. *AstraZeneca and Targacept Announce Remaining TC-5214 Phase 3 Efficacy Studies Do Not Meet Primary Endpoint, Regulatory Filing Will Not Be Pursued*. 2012. [Accessed: December 20, 2016]; Available from: http://www.businesswire.com/news/home/20120320005327/en/AstraZeneca-Targacept-Announce-Remaining-TC-5214-Phase-3.
38. AstraZeneca and Targacept. *AstraZeneca and Targacept Announce Top-line Results from Second Phase 3 Study of TC-5214 as an Adjunct Treatment in Patients with Major Depressive Disorder*. 2011. [Accessed: December 20, 2016]; Available from: http://www.businesswire.com/news/home/20111219006568/en/AstraZeneca-Targacept-Announce-Top-line-Results-Phase-3#.
39. Vieta, E., et al., *Efficacy and tolerability of flexibly-dosed adjunct TC-5214 (dexmecamylamine) in patients with major depressive disorder and inadequate response to prior antidepressant.* Eur Neuropsychopharmacol, 2014. **24**(4): p. 564-74.
40. Criner, G.J., et al., *The National Emphysema Treatment Trial (NETT) Part II: Lessons learned about lung volume reduction surgery.* Am J Respir Crit Care Med, 2011. **184**(8): p. 881-93.
41. Broncus Technologies, *Amendment No. 3 to Form S-1 Registration Statement*. 2008, US Securities and Exchange Commission. [Accessed: December 20, 2016]; Available from: http://www.nasdaq.com/markets/ipos/filing.ashx?filingid=5429619.
42. Cardoso, P.F., et al., *Clinical application of airway bypass with paclitaxel-eluting stents: early results.* J Thorac Cardiovasc Surg, 2007. **134**(4): p. 974-81.
43. Shah, P.L., et al., *Design of the exhale airway stents for emphysema (EASE) trial: an endoscopic procedure for reducing hyperinflation.* BMC Pulm Med, 2011. **11**: p. 1.
44. Shah, P.L., et al., *Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial.* Lancet, 2011. **378**(9795): p. 997-1005.
45. Straface, G., et al., *Herpes simplex virus infection in pregnancy.* Infect Dis Obstet Gynecol, 2012. **2012**: p. 385697.
46. Langenberg, A.G., et al., *A recombinant glycoprotein vaccine for herpes simplex virus type 2: safety and immunogenicity [corrected].* Ann Intern Med, 1995. **122**(12): p. 889-98.
47. Corey, L., et al., *Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection: two randomized controlled trials. Chiron HSV Vaccine Study Group.* Jama, 1999. **282**(4): p. 331-40.
48. Times Staff and Wire Reports. *Chiron Ends Herpes Vaccine Tests*. Los Angeles Times, 1996. [Accessed: December 21, 2016]; Available from: http://articles.latimes.com/1996-11-26/business/fi-3157_1_herpes-transmission.
49. National Center for Chronic Disease Prevention and Health Promotion. *National Diabetes Statistics Report, 2014*. 2014. [Accessed: December 20, 2016]; Available from: https://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
50. Ben Nasr, M., et al., *The rise, fall, and resurgence of immunotherapy in type 1 diabetes.* Pharmacol Res, 2015. **98**: p. 31-8.
51. Ludvigsson, J., et al., *GAD treatment and insulin secretion in recent-onset type 1 diabetes.* N Engl J Med, 2008. **359**(18): p. 1909-20.

52. Ludvigsson, J., et al., *GAD65 antigen therapy in recently diagnosed type 1 diabetes mellitus.* N Engl J Med, 2012. **366**(5): p. 433-42.
53. Centers for Disease Control and Prevention. *Molluscum Contagiosum: Clinical Information*. 2015 [Accessed: December 20, 2016]; Available from: https://www.cdc.gov/poxvirus/molluscum-contagiosum/clinical_information.html.
54. Nguyen, H.P. and S.K. Tyring, *An update on the clinical management of cutaneous molluscum contagiosum.* Skin Therapy Lett, 2014. **19**(2): p. 5-8.
55. Shisler, J.L., *Immune evasion strategies of molluscum contagiosum virus.* Adv Virus Res, 2015. **92**: p. 201-52.
56. 3M Health Care Limited. *Aldara (imiquimod) Cream Prescribing Information*. 2010. [Accessed: December 20, 2016]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020723s022lbl.pdf.
57. Al-Mutairi, N., et al., *Comparative study on the efficacy, safety, and acceptability of imiquimod 5% cream versus cryotherapy for molluscum contagiosum in children.* Pediatr Dermatol, 2010. **27**(4): p. 388-94.
58. US Food and Drug Administration *Clinical Executive Summary - NDA 20723 (Imiquimod 5% cream for Molluscum Contagiosum**)***. 2006. [Accessed: December 21, 2016]; Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM162961.pdf.
59. Kohler, B.A., et al., *Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State.* J Natl Cancer Inst, 2015. **107**(6): p. djv048.
60. Ossovskaya, V., et al., *Abstract #5552: BSI-201 enhances the activity of multiple classes of cytotoxic agents and irradiation in triple negative breast cancer.* Cancer Research, 2009. **69**(9 Supplement): p. 5552-5552.
61. Licht, S., et al., *Abstract A226: Mechanism of action of iniparib: Stimulation of reactive oxygen species (ROS) production in an iniparib-sensitive breast cancer cell line.* Molecular Cancer Therapeutics, 2011. **10**(11 Supplement): p. A226-A226.
62. O'Shaughnessy, J., et al., *Iniparib plus chemotherapy in metastatic triple-negative breast cancer.* N Engl J Med, 2011. **364**(3): p. 205-14.
63. O'Shaughnessy, J., et al., *Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer.* J Clin Oncol, 2014. **32**(34): p. 3840-7.
64. Wijesekera, L.C. and P.N. Leigh, *Amyotrophic lateral sclerosis.* Orphanet J Rare Dis, 2009. **4**: p. 3.
65. Kinsley L and S. T., *Amyotrophic Lateral Sclerosis Overview. 2001 Mar 23 [Updated 2015 Feb 12]*, in *GeneReviews® [Internet]*, Pagon RA, et al., Editors. 2001, University of Washington, Seattle; 1993-2016.: Seattle (WA). Available from: https://www.ncbi.nlm.nih.gov/books/NBK1450/.
66. US National Library of Medicine. *Amyotrophic Lateral Sclerosis*. 2016 [Accessed: December 21, 2016]; Available from: https://ghr.nlm.nih.gov/condition/amyotrophic-lateral-sclerosis.
67. Jablonski, M., et al., *ABC transporter-driven pharmacoresistance in Amyotrophic Lateral Sclerosis.* Brain Res, 2015. **1607**: p. 1-14.
68. Sanofi-Aventis. *Rilute (riluzole) Prescribing Information*. 2009. [Accessed: December 21, 2016]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020599s013lbl.pdf.
69. Miller, R.G., J.D. Mitchell, and D.H. Moore, *Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND).* Cochrane Database Syst Rev, 2012(3): p. Cd001447.
70. Fornai, F., et al., *Lithium delays progression of amyotrophic lateral sclerosis.* Proc Natl Acad Sci U S A, 2008. **105**(6): p. 2052-7.

71. Al-Chalabi, A., et al., *Protocol for a double-blind randomised placebo-controlled trial of lithium carbonate in patients with amyotrophic lateral sclerosis (LiCALS) [Eudract number: 2008-006891-31].* BMC Neurol, 2011. **11**: p. 111.
72. Morrison, K.E., et al., *Lithium in patients with amyotrophic lateral sclerosis (LiCALS): a phase 3 multicentre, randomised, double-blind, placebo-controlled trial.* Lancet Neurol, 2013. **12**(4): p. 339-45.
73. Molina, J.R., et al., *Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship.* Mayo Clin Proc, 2008. **83**(5): p. 584-94.
74. Finn, O.J., *Cancer immunology.* N Engl J Med, 2008. **358**(25): p. 2704-15.
75. Vansteenkiste, J., et al., *Adjuvant MAGE-A3 immunotherapy in resected non-small-cell lung cancer: phase II randomized study results.* J Clin Oncol, 2013. **31**(19): p. 2396-403.
76. Tyagi, P. and B. Mirakhur, *MAGRIT: the largest-ever phase III lung cancer trial aims to establish a novel tumor-specific approach to therapy.* Clin Lung Cancer, 2009. **10**(5): p. 371-4.
77. Vansteenkiste, J.F., et al., *1173O MAGRIT, A Double-Blind, Randomized, Placebo-Controlled Phase Iii Study To Assess The Efficacy Of The Recmage-A3 + As15 Cancer Immunotherapeutic As Adjuvant Therapy In Patients With Resected Mage-A3-Positive Non-Small Cell Lung Cancer (NSCLC).* Annals of Oncology, 2014. **25**(suppl 4): p. iv409.
78. Hartmann-Boyce, J., et al., *Nicotine vaccines for smoking cessation.* Cochrane Database Syst Rev, 2012(8): p. Cd007072.
79. Fahim, R.E., P.D. Kessler, and M.W. Kalnik, *Therapeutic vaccines against tobacco addiction.* Expert Rev Vaccines, 2013. **12**(3): p. 333-42.
80. Hatsukami, D.K., et al., *Immunogenicity and smoking-cessation outcomes for a novel nicotine immunotherapeutic.* Clin Pharmacol Ther, 2011. **89**(3): p. 392-9.
81. Fahim, R.E., et al., *Nicotine vaccines.* CNS Neurol Disord Drug Targets, 2011. **10**(8): p. 905-15.
82. Nabel, G.J., et al., *Direct gene transfer with DNA-liposome complexes in melanoma: expression, biologic activity, and lack of toxicity in humans.* Proc Natl Acad Sci U S A, 1993. **90**(23): p. 11307-11.
83. Bedikian, A.Y., et al., *A phase 2 study of high-dose Allovectin-7 in patients with advanced metastatic melanoma.* Melanoma Res, 2010. **20**(3): p. 218-26.
84. Agarwala, S.S., *Intralesional therapy for advanced melanoma: promise and limitation.* Curr Opin Oncol, 2015. **27**(2): p. 151-6.
85. Jones, P.B., et al., *Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1).* Arch Gen Psychiatry, 2006. **63**(10): p. 1079-87.
86. Seida, J.C., et al., *AHRQ Comparative Effectiveness Reviews*, in *First- and Second-Generation Antipsychotics for Children and Young Adults*. 2012, Agency for Healthcare Research and Quality (US): Rockville (MD).
87. Valenstein, M., et al., *Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review.* J Clin Psychiatry, 2006. **67**(10): p. 1542-50.
88. Eli Lilly and Company. *Psychopharmacologic Drugs Advisory Committee Briefing Document: Zyprexa® Olanzapine Pamoate (OP) Depot*. 2008. [Accessed: December 21, 2016]; Available from: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4338b1-03-Lilly.pdf.
89. US Food and Drug Administration. *Agency Background Package: Psychopharmacologic Drugs Advisory Committee: Zyprexa® Olanzapine Pamoate (OP) Depot*. 2008. [Accessed: December 21, 2016]; Available from: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4338b1-01-FDA.pdf.

90. US Food and Drug Administration. *Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting.* 2008. [Accessed: December 21, 2016]; Available from: http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4338m1-final.pdf.
91. *Risk Evaluation and Mitigation Strategy (REMS), Zyprexa Relprevv Patient Care Program NDA 22173, Zyprexa Relprevv (olanzapine), For Extended Release Injectable Suspension. Initial REMS approval 12/2009, Most Recent Modification 10/2014*. 2014. [Accessed: December 22, 2016]; Available from: http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm202330.pdf.
92. Maisel, A.S., et al., *Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure.* N Engl J Med, 2002. **347**(3): p. 161-7.
93. McMurray, J.J., et al., *Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure.* Circ Heart Fail, 2008. **1**(1): p. 17-24.
94. Gheorghiade, M., et al., *Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial.* Jama, 2013. **309**(11): p. 1125-35.
95. Kaul, U., et al., *Cobalt chromium stent with antiproliferative for restenosis trial in India (COSTAR I).* Indian Heart J, 2007. **59**(2): p. 165-72.
96. US Food and Drug Administration. *Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US.* 2012. [Accessed: December 21, 2016]; Available from: http://www.elsevierbi.com/~/media/Supporting%20Documents/The%20Gray%20Sheet/38/20/FDA_EU_Devices_Report.pdf.
97. Krucoff, M.W., et al., *A novel bioresorbable polymer paclitaxel-eluting stent for the treatment of single and multivessel coronary disease: primary results of the COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II study.* J Am Coll Cardiol, 2008. **51**(16): p. 1543-52.
98. Gualberto, A. and D.D. Karp, *Development of the monoclonal antibody figitumumab, targeting the insulin-like growth factor-1 receptor, for the treatment of patients with non-small-cell lung cancer.* Clin Lung Cancer, 2009. **10**(4): p. 273-80.
99. Di Maio, M. and G.V. Scagliotti, *The lesson learned from figitumumab clinical program and the hope for better results in squamous lung cancer.* Transl Lung Cancer Res, 2015. **4**(1): p. 15-7.
100. Karp, D.D., et al., *Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer.* J Clin Oncol, 2009. **27**(15): p. 2516-22.
101. Scagliotti, G.V., et al., *Randomized, phase III trial of figitumumab in combination with erlotinib versus erlotinib alone in patients with nonadenocarcinoma nonsmall-cell lung cancer.* Ann Oncol, 2015. **26**(3): p. 497-504.
102. Langer, C.J., et al., *Randomized, phase III trial of first-line figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with advanced non-small-cell lung cancer.* J Clin Oncol, 2014. **32**(19): p. 2059-66.
103. *Retraction. "Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer".* J Clin Oncol, 2012. **30**(33): p. 4179.
104. Mayer, S.A., et al., *Recombinant activated factor VII for acute intracerebral hemorrhage.* N Engl J Med, 2005. **352**(8): p. 777-85.
105. Mayer, S.A., et al., *Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage.* N Engl J Med, 2008. **358**(20): p. 2127-37.
106. Alzheimer's Association. *What Is Alzheimer's?* 2016 [Accessed: December 20, 2016]; Available from: http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp.

107. Henley, D.B., et al., *Development of semagacestat (LY450139), a functional gamma-secretase inhibitor, for the treatment of Alzheimer's disease.* Expert Opin Pharmacother, 2009. **10**(10): p. 1657-64.
108. Fleisher, A.S., et al., *Phase 2 safety trial targeting amyloid beta production with a gamma-secretase inhibitor in Alzheimer disease.* Arch Neurol, 2008. **65**(8): p. 1031-8.
109. Doody, R.S., et al., *A phase 3 trial of semagacestat for treatment of Alzheimer's disease.* N Engl J Med, 2013. **369**(4): p. 341-50.
110. American Heart Association. *What Your Cholesterol Levels Mean*. 2016 [Accessed: December 21, 2016]; Available from: http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp#.
111. McKenney, J.M., et al., *Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels on a background of atorvastatin.* J Am Coll Cardiol, 2006. **48**(9): p. 1782-90.
112. Davidson, M.H., et al., *Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels.* J Am Coll Cardiol, 2006. **48**(9): p. 1774-81.
113. Berenson, A. *Pfizer Ends Studies on Drug for Heart Disease*. The New York Times, 2006. [Accessed: December 21, 2016]; Available from: http://www.nytimes.com/2006/12/03/health/03pfizer.html?_r=2&th&emc=th&oref=slogin&.
114. Tanne, J.H., *Pfizer stops clinical trials of heart drug.* Bmj, 2006. **333**(7581): p. 1237.
115. Barter, P.J., et al., *Effects of torcetrapib in patients at high risk for coronary events.* N Engl J Med, 2007. **357**(21): p. 2109-22.
116. van Hal, S.J., et al., *Predictors of mortality in Staphylococcus aureus Bacteremia.* Clin Microbiol Rev, 2012. **25**(2): p. 362-86.
117. Fowler, V.G., Jr. and R.A. Proctor, *Where does a Staphylococcus aureus vaccine stand?* Clin Microbiol Infect, 2014. **20 Suppl 5**: p. 66-75.
118. Harro, C.D., et al., *The immunogenicity and safety of different formulations of a novel Staphylococcus aureus vaccine (V710): results of two Phase I studies.* Vaccine, 2012. **30**(9): p. 1729-36.
119. Moustafa, M., et al., *Phase IIa study of the immunogenicity and safety of the novel Staphylococcus aureus vaccine V710 in adults with end-stage renal disease receiving hemodialysis.* Clin Vaccine Immunol, 2012. **19**(9): p. 1509-16.
120. Fowler, V.G., et al., *Effect of an investigational vaccine for preventing Staphylococcus aureus infections after cardiothoracic surgery: a randomized trial.* Jama, 2013. **309**(13): p. 1368-78.
121. Reid, K. *Merck ends trial of Intercell's MRSA vaccine*. Reuters, 2011. [Accessed: December 21, 2016]; Available from: http://www.reuters.com/article/us-intercell-merck-idUSTRE75711P20110608.
122. Fleming, T.R. and D.L. DeMets, *Surrogate end points in clinical trials: are we being misled?* Ann Intern Med, 1996. **125**(7): p. 605-13.
123. Doll, R., *Controlled trials: the 1948 watershed.* BMJ, 1998. **317**(7167): p. 1217-20.
124. US Food and Drug Administration *Draft Guidance for Industry and Food and Drug Administration Staff: Adaptive Designs for Medical Device Clinical Studies*. 2015. [Accessed: December 22, 2016]; Available from: http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446729.pdf.
125. US Food and Drug Administration *Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. 2012. [Accessed: December

22, 2016]; Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf.
126. US Food and Drug Administration *Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials*. 2001. [Accessed: December 22, 2016]; Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073139.pdf.
127. *Adequate and well-controlled studies, 21 C.F.R. § 314.126(b)(2)(v)*. 2002. [Accessed: December 22, 2016]; Available from: http://www.ecfr.gov/cgi-bin/text-idx?SID=95ba32c632b35627b19593e00e944aef&mc=true&node=se21.5.314_1126&rgn=div8.
128. Rising, K., P. Bacchetti, and L. Bero, *Reporting bias in drug trials submitted to the Food and Drug Administration: review of publication and presentation.* PLoS Med, 2008. **5**(11): p. e217; discussion e217.
129. Lurie, P., et al., *Comparison of content of FDA letters not approving applications for new drugs and associated public announcements from sponsors: cross sectional study.* The British Medical Journal (BMJ), 2015. **350**(h2758).

Footnote 11

Centers for Disease Control and Prevention

Attention-Deficit / Hyperactivity Disorder (ADHD)

Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD: United States, 2003—2011

Researchers from the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration have published a study: "Trends in the Parent-Report of Health Care Provider-Diagnosed and Medicated ADHD: United States, 2003—2011." Read the abstract [1]. See below for a summary of the findings from this article.

Health care providers who care for children with attention-deficit/hyperactivity disorder (ADHD) and public health practitioners should be aware that an estimated two million more US children were reported by their parents to be diagnosed by a health care provider with ADHD and a million more were reported to be taking medication for ADHD in 2011, compared to 2003. These health professionals should also be aware of the changing patterns of ADHD in the United States.

About attention-deficit/hyperactivity disorder and this study:

ADHD is a neurobehavioral disorder of childhood that often persists into adulthood. CDC uses national surveys that ask parents about their child's health to monitor the number of children with ADHD and the treatment patterns for these children. The largest of these surveys is the National Survey of Children's Health, which has been collected every four years since 2003. Previous results from the 2003 and 2007 surveys found that 7.8% and 9.5% of US children aged 4-17 years were reported by their parents to have ever been diagnosed with ADHD by a health care provider in 2003 and 2007, respectively. The current study looked at data from the third National Survey of Children's Health, conducted in 2011-2012. The findings tell us more about ADHD diagnosis and treatment patterns, and reflect the substantial impact that ADHD has on families.

Learn more about the data source: National Survey of Children's Health

Important findings from this study include:

More than 1 in 10 (11%) US school-aged children had received an ADHD diagnosis by a health care provider by 2011, as reported by parents.

- 6.4 million children reported by parents to have ever received a health care provider diagnosis of ADHD , including:
  - 1 in 5 high school boys
  - 1 in 11 high school girls

The percentage of US children 4-17 years of age with an ADHD diagnosis by a health care provider, as reported by parents, continues to increase.

- A history of ADHD diagnosis by a health care provider increased by 42% between 2003 and 2011:
  - 7.8% had ever had a diagnosis in 2003
  - 9.5% had ever had a diagnosis in 2007
  - 11.0% had ever had a diagnosis in 2011
- Average annual increase was approximately 5% per year

The percentage of children 4-17 years of age taking medication for ADHD, as reported by parents, increased by 28% between 2007 and 2011.

- Percentage of children taking medication for ADHD was:

        - 4.8% in 2007
        - 6.1% in 2011
    - Average annual increase was approximately 7% per year

The average age of ADHD diagnosis was 7 years of age, but children reported by their parents as having more severe ADHD were diagnosed earlier.

- 8 years of age was the average age of diagnosis for children reported as having ***mild*** ADHD
- 7 years of age was the average age of diagnosis for children reported as having ***moderate*** ADHD
- 5 years of age was the average age of diagnosis for children reported as having ***severe*** ADHD

More US children were reported by their parents to be receiving ADHD treatment in 2011 compared to 2007, however treatment gaps may exist.

- In 2011, as many as 17.5% of children with current ADHD were reported by their parents as **not** receiving either medication for ADHD or mental health counseling
- More than one-third of children reported by their parents as **not** receiving treatment were also reported to have moderate or severe ADHD

The patterns in ADHD diagnosis and medication treatment showed increases in the percentages overall, however some new patterns emerged between 2007 and 2011.

- The percentage of children reported by their parents to have a history of health care provider diagnosed ADHD increased for most demographic groups (for example, across racial groups, boys and girls) from 2003 to 2011; however,
- Between 2007 and 2011, the percentage of children reported by their parents to have a history of a health care provider diagnosed ADHD:
    - Was similar among older teens
    - Decreased among multiracial children and children of other races when compared to black or white children

The number of US families impacted by ADHD continues to increase.

- An estimated 2 million more children were reported by their parents to be diagnosed by a health care professional with ADHD in 2011, compared to 2003
    - By 2011, 6.4 million children were reported by their parents to be diagnosed by a health professional with ADHD compared to 4.4 million in 2003
- An estimated 1 million more children were reported by their parents to be taking medication for ADHD in 2011, compared to 2003.
    - By 2011, 3.5 million children were reported by their parents to be taking medication for ADHD compared to 2.5 million in 2003

ADHD: CDC's Activities

CDC monitors the number of children who have been diagnosed with ADHD through the use of national survey data. Including questions about ADHD on national or regional surveys helps us learn more about the number of children with ADHD, their use of ADHD treatments, and the impact of ADHD on children and their families. CDC has previously used national survey data to document increasing estimates of the number of children with ADHD from 2003-2007.[2] CDC has also used these data to estimate the percentage of children taking medication for ADHD, nationally and by state.[3]

CDC also conducts community-based studies to better understand the impact of ADHD. The Project to Learn about ADHD in Youth (PLAY) study methods have been implemented in four community sites. Information from the PLAY study helps us better understand ADHD as well as the needs of children and families living with ADHD.

CDC supports the National Resource Center on ADHD, a program of Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), which is a Public Health Practice and Resource Center. Their web site (http://www.help4adhd.org/NRC.aspx) has links to information based on the current best medical evidence about the care for people with ADHD and their families. The National Resource Center operates a call center with trained, bilingual staff to answer questions about ADHD. Their phone number is 1-800-233-4050.

More Information

To learn more about ADHD, please visit https://www.cdc.gov/adhd.

References

1. Visser S, Danielson M, Bitsko R, et al. Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD disorder: United States, 2003–2011. J Am Acad Child Adolesc Psychiatry. 2014,53(1):34–46.e2.
2. Centers for Disease Control and Prevention. Increasing Prevalence of Parent-Reported Attention-Deficit/Hyperactivity Disorder Among Children — United States, 2003 and 2007. *MMWR.* 2010;59(44):1439-1443.
3. Visser SN, Blumberg SJ, Danielson ML, Bitsko RH, Kogan MD. State-Based and Demographic Variation in Parent-Reported Medication Rates for Attention-Deficit/Hyperactivity Disorder, 2007-2008. *Prev Chronic Dis.* Jan 2013;10:E09.

Page last reviewed: August 29, 2019

How are learning disabilities diagnosed?

En Español

Learning disabilities are often identified once a child is in school. The school may use a process called “response to intervention” to help identify children with learning disabilities. Special tests are required to make a diagnosis.

Response to Intervention

Response to intervention usually involves the following[1]:

- Monitoring all students’ progress closely to identify possible learning problems
- Providing children who are having problems with help on different levels, or tiers
- Moving children to tiers that provide increasing support if they do not show sufficient progress

Students who are struggling in school can also have individual evaluations. An evaluation can[2]:

- Identify whether a child has a learning disability
- Determine a child’s eligibility under federal law for special education services
- Help develop an individualized education plan (IEP) that outlines help for a child who qualifies for special education services
- Establish benchmarks to measure the child’s progress

A full evaluation for a learning disability includes the following[3]:

- A medical exam, including a neurological exam, to rule out other possible causes of the child’s difficulties. These might include emotional disorders, intellectual and developmental disabilities, and brain diseases.
- Reviewing the child’s developmental, social, and school performance
- A discussion of family history
- Academic and psychological testing

Usually, several specialists work as a team to do the evaluation. The team may include a psychologist, a special education expert, and a speech-language pathologist. Many schools also have reading specialists who can help diagnose a reading disability.[4]

Role of School Psychologists

School psychologists are trained in both education and psychology. They can help diagnose students with learning disabilities and help the student and his or her parents and teachers come up with plans to improve learning.[5]

Role of Speech-Language Pathologists

All speech-language pathologists are trained to diagnose and treat speech and language disorders. A speech-language pathologist can do a language evaluation and assess the child's ability to organize his or her thoughts and possessions. The speech-language pathologist may evaluate the child's learning skills, such as understanding directions, manipulating sounds, and reading and writing.[6]

Citations

1. National Center for Learning Disabilities. (n.d.). *What is RTI?* Retrieved March 8, 2017, from http://www.rtinetwork.org/learn/what/whatisrti (http://www.rtinetwork.org/learn/what/whatisrti)
2. Learning Disabilities Association of America. (2001). *Assessment & evaluation.* Retrieved March 8, 2017, from https://ldaamerica.org/category/assessment-evaluation/?audience=Parents (https://ldaamerica.org/category/assessment-evaluation/?audience=Parents)
3. National Library of Medicine. (2015). *Developmental reading disorder.* Retrieved March 8, 2017, from http://www.nlm.nih.gov/medlineplus/ency/article/001406.htm (http://www.nlm.nih.gov/medlineplus/ency/article/001406.htm)
4. Learning Disabilities Association of America. (n.d.). *Eligibility: Determining whether a child is eligible for special education services.* Retrieved March 8, 2017, from https://ldaamerica.org/eligibility-determining-whether-a-child-is-eligible-for-special-education-services/ (https://ldaamerica.org/eligibility-determining-whether-a-child-is-eligible-for-special-education-services/) (PDF 86 KB)
5. National Association of School Psychologists. (n.d.). *Who are school psychologists?* Retrieved March 8, 2017, from http://www.nasponline.org/about-school-psychology/who-are-school-psychologists (http://www.nasponline.org/about-school-psychology/who-are-school-psychologists)
6. American Speech-Language-Hearing Association. (n.d.). *Learning disabilities.* Retrieved August 24, 2018, from http://www.asha.org/public/speech/disorders/LBLD.htm (http://www.asha.org/public/speech/disorders/LBLD.htm)

Related A-Z Topics

Reading and Reading Disorders (/health/topics/reading)

Early Learning (/health/topics/early-learning)

Neuroscience (/health/topics/neuro)

NICHD News and Features

Item of Interest: NICHD Selects Six Infrastructure Centers to Promote Rehabilitation Research (/newsroom/news/071420-rehabilitation-research)

Item of Interest: James A. Griffin, Ph.D., named new Chief of NICHD's Child Development and Behavior Branch (/newsroom/news/040120-griffin)

Media Advisory: Gene mutation enhances cognitive flexibility in mice, NIH study suggests (/newsroom/news/032720-cognitive-flexibility)

All related news (/newsroom/news?topic=learning)

- **Lung function tests (spirometry).** Doctors diagnose asthma with the same tests used to identify the disease in adults. Spirometry measures how much air your child can exhale and how quickly. Your child might have lung function tests at rest, after exercising and after taking asthma medication.

  Another lung function test is brochoprovocation. Using spirometry, this test measures how your lungs react to certain provocations, such as exercise or exposure to cold air.

- **Exhaled nitric oxide test.** If the diagnosis of asthma is uncertain after lung function tests, your doctor might recommend measuring the level of nitric oxide in an exhaled sample of your child's breath. Nitric oxide testing can also help determine whether steroid medications might be helpful for your child's asthma.

The asthma tests used, however, aren't accurate before 5 years of age. For younger children, your doctor will rely on information you and your child provide about symptoms. Sometimes a diagnosis can't be made until later, after months or even years of observing symptoms.

Allergy tests for allergic asthma

If your child seems to have asthma that's triggered by allergies, the doctor might recommend allergy skin testing. During a skin test, the skin is pricked with extracts of common allergy-causing substances, such as animal dander, mold or dust mites, and observed for signs of an allergic reaction.

More Information

Will my child outgrow asthma?

Treatment

Initial treatment depends on the severity of your child's asthma. The goal of asthma treatment is to keep symptoms under control, meaning that your child has:

- Minimal or no symptoms
- Few or no asthma flare-ups
- No limitations on physical activities or exercise

Childhood asthma

Request an Appointment

Symptoms & causes Diagnosis & treatment Doctors & departments

Diagnosis

Print

Asthma can be hard to diagnose. Your child's doctor will consider the symptoms and their frequency and your child's medical history. Your child might need tests to rule out other conditions and to identify the most likely cause of the symptoms.

A number of childhood conditions can have symptoms similar to those caused by asthma. To complicate the issue further, these conditions also commonly occur with asthma. So your child's doctor will have to determine whether your child's symptoms are caused by asthma, a condition other than asthma, or both asthma and another condition.

Conditions that can cause asthma-like symptoms include:

- Rhinitis
- Sinusitis
- Acid reflux or gastroesophageal reflux disease (GERD)
- Airway abnormalities
- Dysfunctional breathing
- Respiratory tract infections such as bronchiolitis and respiratory syncytial virus (RSV)

The following are tests your child might need.

- Minimal use of quick-relief (rescue) inhalers, such as albuterol (ProAir HFA, Ventolin HFA, others)
- Few or no side effects from medications

Treating asthma involves both preventing symptoms and treating an asthma attack in progress. The right medication for your child depends on a number of things, including age, symptoms, asthma triggers and what seems to work best to keep his or her asthma under control.

For children younger than age 3 who have mild symptoms of asthma, the doctor might use a wait-and-see approach. This is because the long-term effects of asthma medication on infants and young children aren't clear.

However, if an infant or toddler has frequent or severe wheezing episodes, a medication might be prescribed to see if it improves symptoms.

Long-term control medications

Preventive, long-term control medications reduce the inflammation in your child's airways that leads to symptoms. In most cases, these medications need to be taken daily.

Types of long-term control medications include:

- **Inhaled corticosteroids.** These medications include fluticasone (Flovent Diskus, Flovent HFA), budesonide (Pulmicort Flexhaler), mometasone (Asmanex HFA), ciclesonide (Alvesco), beclomethasone (Qvar Redihaler) and others. Your child might need to use these medications for several days to weeks before getting the full benefit.

  Long-term use of these medications has been associated with slightly slowed growth in children, but the effect is minor. In most cases, the benefits of good asthma control outweigh the risks of possible side effects.
- **Leukotriene modifiers.** These oral medications include montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo). They help prevent asthma symptoms for up to 24 hours.
- **Combination inhalers.** These medications contain an inhaled corticosteroid plus a long-acting beta agonist (LABA). They include fluticasone and salmeterol (Advair Diskus, Advair HFA), budesonide and formoterol (Symbicort), fluticasone and vilanterol (Breo Ellipta), and mometasone and formoterol (Dulera).

  In some situations, long-acting beta agonists have been linked to severe asthma attacks. For this reason, LABA medications should

always be given to a child with an inhaler that also contains a corticosteroid. These combination inhalers should be used only for asthma that's not well-controlled by other medications.

- **Theophylline.** This is a daily pill that helps keep the airways open. Theophylline (Theo-24) relaxes the muscles around the airways to make breathing easier. It's mostly used with inhaled steroids. If you take this drug, you'll need to have your blood checked regularly.
- **Immunomodulatory agents.** Mepolizumab (Nucala), dupilumab (Dupixent) and benralizumab (Fasenra) might be appropriate for children over the age of 12 who have severe eosinophilic asthma. Omalizumab (Xolair) can be considered for children age 6 or older who have moderate to severe allergic asthma.

Quick-relief medications

Quick-relief medications quickly open swollen airways. Also called rescue medications, quick-relief medications are used as needed for rapid, short-term symptom relief during an asthma attack — or before exercise if your child's doctor recommends it.

Types of quick-relief medications include:

- **Short-acting beta agonists.** These inhaled bronchodilator medications can rapidly ease symptoms during an asthma attack. They include albuterol (ProAir HFA, Ventolin HFA, others) and levalbuterol (Xopenex HFA). These medications act within minutes, and effects last several hours.
- **Oral and intravenous corticosteroids.** These medications relieve airway inflammation caused by severe asthma. Examples include prednisone and methylprednisolone. They can cause serious side effects when used long term, so they're only used to treat severe asthma symptoms on a short-term basis.

Treatment for allergy-induced asthma

If your child's asthma is triggered or worsened by allergies, your child might benefit from allergy treatment, such as the following, as well:

- **Omalizumab (Xolair).** This medication is for people who have allergies and severe asthma. It reduces the immune system's reaction to allergy-causing substances, such as pollen, dust mites and pet dander. Xolair is delivered by injection every two to four weeks.
- **Allergy medications.** These include oral and nasal spray antihistamines and decongestants as well as corticosteroid, cromolyn and ipratropium nasal sprays.

- **Allergy shots (immunotherapy).** Immunotherapy injections are generally given once a week for a few months, then once a month for a period of three to five years. Over time, they gradually reduce your child's immune system reaction to specific allergens.

Don't rely only on quick-relief medications

Long-term asthma control medications such as inhaled corticosteroids are the cornerstone of asthma treatment. These medications keep asthma under control and make it less likely that your child will have an asthma attack.

If your child does have an asthma flare-up, a quick-relief (rescue) inhaler can ease symptoms right away. But if long-term control medications are working properly, your child shouldn't need to use a quick-relief inhaler very often.

Keep a record of how many puffs your child uses each week. If he or she frequently needs to use a quick-relief inhaler, take your child to see the doctor. You probably need to adjust the long-term control medication.

Inhaled medication devices

Inhaled short- and long-term control medications are used by inhaling a measured dose of medication.

- **Older children and teens** might use a small, hand-held device called a pressurized metered dose inhaler or an inhaler that releases a fine powder.
- **Infants and toddlers** need to use a face mask attached to a metered dose inhaler or a nebulizer to get the correct amount of medication.
- **Babies** need to a use a device that turns liquid medication into fine droplets (nebulizer). Your baby wears a face mask and breathes normally while the nebulizer delivers the correct dose of medication.

Asthma action plan

Work with your child's doctor to create a written asthma action plan. This can be an important part of treatment, especially if your child has severe asthma. An asthma action plan can help you and your child:

- Recognize when you need to adjust long-term control medications
- Determine how well treatment is working

- Identify the signs of an asthma attack and know what to do when one occurs
- Know when to call a doctor or seek emergency help

Children who have enough coordination and understanding might use a hand-held device to measure how well they can breathe (peak flow meter). A written asthma action plan can help you and your child remember what to do when peak flow measurements reach a certain level.

The action plan might use peak flow measurements and symptoms to categorize your child's asthma into zones, such as the green zone, yellow zone and red zone. These zones correspond to well-controlled symptoms, somewhat-controlled symptoms and poorly controlled symptoms. This makes tracking your child's asthma easier.

Your child's symptoms and triggers are likely to change over time. You'll need to observe symptoms and work with the doctor to adjust medications as needed.

If your child's symptoms are completely controlled for a time, your child's doctor might recommend lowering doses or stopping asthma medications (step-down treatment). If your child's asthma isn't as well-controlled, the doctor might want to increase, change or add medications (step-up treatment).

More Information

Asthma in children under 5

Treating asthma in children age 12 and older

Treating asthma in children ages 5 to 11

Request an Appointment at Mayo Clinic

Clinical trials

Explore Mayo Clinic studies testing new treatments, interventions and tests as a means to prevent, detect, treat or manage this disease.

Lifestyle and home remedies

Taking steps to reduce your child's exposure to asthma triggers will lessen the possibility of asthma attacks. Steps to help avoid triggers vary depending on what triggers your child's asthma. Here are some things that may help:

- **Maintain low humidity at home.** If you live in a damp climate, talk to your child's doctor about using a device to keep the air drier (dehumidifier).
- **Keep indoor air clean.** Have a heating and air conditioning professional check your air conditioning system every year. Change the filters in your furnace and air conditioner according to the manufacturer's instructions. Also consider installing a small-particle filter in your ventilation system.
- **Reduce pet dander.** If your child is allergic to dander, it's best to avoid pets with fur or feathers. If you have pets, regularly bathing or grooming your pets also might reduce the amount of dander. Keep pets out of your child's room.
- **Use your air conditioner**. Air conditioning helps reduce the amount of airborne pollen from trees, grasses and weeds that finds its way indoors. Air conditioning also lowers indoor humidity and can reduce your child's exposure to dust mites. If you don't have air conditioning, try to keep your windows closed during pollen season.
- **Keep dust to a minimum.** Reduce dust that can aggravate nighttime symptoms by replacing certain items in your bedroom. For example, encase pillows, mattresses and box springs in dustproof covers. Consider removing carpeting and installing hard flooring, particularly in your child's bedroom. Use washable curtains and blinds.
- **Clean regularly.** Clean your home at least once a week to remove dust and allergens.
- **Reduce your child's exposure to cold air.** If your child's asthma is worsened by cold, dry air, wearing a face mask outside can help.

More Information

Childhood asthma action plan

Asthma and hard flooring

Alternative medicine

While some alternative remedies are used for asthma, in most cases more research is needed to see how well they work and to determine possible side effects. Alternative treatments to consider include:

- **Breathing techniques.** These include structured breathing programs, such as the Buteyko breathing technique, the Papworth method and yoga breathing exercises (pranayama).
- **Relaxation techniques.** Techniques such as meditation, biofeedback, hypnosis and progressive muscle relaxation might help with asthma by reducing tension and stress.
- **Herbal remedies and supplements.** A few herbal remedies have been tried for asthma, including black seed, fish oil and magnesium. However, further studies are needed to assess their benefit and safety.

  Herbs and supplements can have side effects and can interact with other medications your child is taking. Talk to your child's doctor before trying any herbs or supplements.

Coping and support

It can be stressful to help your child manage asthma. Keep these tips in mind to make life as normal as possible:

- **Make treatment a regular part of life.** If your child has to take daily medication, don't make a big deal out of it — it should be as routine as eating breakfast or brushing teeth.
- **Use a written asthma action plan.** Work with your child's doctor to develop your child's action plan, and give a copy to all of your child's caregivers, such as child care providers, teachers, coaches and the parents of your child's friends.

  Following a written plan can help you and your child identify symptoms early, providing important information on how to treat your child's asthma from day to day and how to deal with an asthma attack.
- **Be encouraging.** Focus attention on what your child can do, not on limitations. Involve teachers, school nurses, coaches, relatives and friends in helping your child manage asthma.

  Encourage normal play and activity. Don't limit your child's activities out of fear of an asthma attack — work with your child's doctor to control exercise-induced symptoms.
- **Be calm and in control.** Don't get rattled if asthma symptoms worsen. Focus on your child's asthma action plan, and involve your child in each step so that he or she understands what's happening.

- **Talk to other parents of children with asthma.** Chat rooms and message boards on the internet or a local support group can connect you with parents facing similar challenges.
- **Help your child connect with others who have asthma.** Send your child to "asthma camp" or find other organized activities for children with asthma. This can help your child feel less isolated and gain a better understanding of asthma and its treatment.

Preparing for your appointment

You're likely to start by taking your child to your family doctor or your child's pediatrician. However, when you call to set up an appointment, you may be referred to an allergist, lung doctor (pulmonologist) or other specialist. Here's some information to help you get ready for your child's appointment.

What you can do

Make a list of:

- **Your child's symptoms,** how severe they are and when they occur. Note when symptoms bother your child most — for example, if symptoms tend to get worse at certain times of the day; during certain seasons; when your child is exposed to cold air, pollen or other triggers; or when he or she is playing hard or participating in sports.
- **Key personal information,** including any major stresses or recent life changes your child has had.
- **All medications,** vitamins and supplements your child takes, including doses.
- **Write down questions to ask** the doctor.

For asthma or asthma-like symptoms, questions to ask your doctor include:

- Is asthma the most likely cause of my child's breathing problems?
- What else could be causing my child's symptoms?
- What tests does my child need?
- Is my child's condition likely temporary or chronic?
- What treatment do you suggest?
- My child has these other health conditions. How can we best manage them together?
- Are there restrictions my child needs to follow?
- Should my child see a specialist?

- Are there brochures or other printed materials I can have? What websites do you recommend?

Don't hesitate to ask other questions.

What to expect from your child's doctor

The doctor is likely to ask questions, including:

- When did you notice your child's symptoms?
- Does your child have difficulty breathing most of the time or only at certain times or in certain situations?
- Does your child have allergies such as hay fever?
- What, if anything, appears to worsen your child's symptoms?
- What, if anything, seems to improve your child's symptoms?
- Do allergies or asthma run in your child's family?

By Mayo Clinic Staff

Related

Asthma and hard flooring

Asthma in children under 5

Childhood asthma action plan

Show more related content

Products & Services

Book: Mayo Clinic Guide to Raising a Healthy Child

Childhood asthma

Symptoms & causes

Diagnosis & treatment

Doctors & departments

CON-20157223

Footnote 12

HHS Public Access

Author manuscript

JAMA Pediatr. Author manuscript; available in PMC 2019 August 05.

Published in final edited form as:

JAMA Pediatr. 2019 January 01; 173(1): 60–67. doi:10.1001/jamapediatrics.2018.3227.

Duration of Pediatric Clinical Trials Submitted to the US Food and Drug Administration

Kanecia O. Zimmerman, MD, MPH, **P. Brian Smith, MD, MPH, MHS**, **Ann W. McMahon, MD, MS**, **Jean Temeck, MD**, **Debbie Avant, RPh**, **Dianne Murphy, MD**, **Susan McCune, MD**

Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina (Zimmerman, Smith); Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina (Zimmerman, Smith); Office of Pediatric Therapeutics, US Food and Drug Administration, Silver Spring, Maryland (McMahon, Temeck, Avant, Murphy, McCune).

Abstract

IMPORTANCE—The increasing prevalence of pediatric chronic disease has resulted in increased exposure to long-term drug therapy in children. The duration of recently completed drug trials that support approval for drug therapy in children with chronic diseases has not been systematically evaluated. Such information is a vital first step in forming safety pharmacovigilance strategies for drugs used for long-term therapy in children.

OBJECTIVE—To characterize the duration of clinical trials submitted to the US Food and Drug Administration (FDA) for pediatric drug approvals, with a focus on drugs used for long-term therapy.

DESIGN AND SETTING—A review was performed of all safety and efficacy clinical trials conducted under the Best Pharmaceuticals for Children Act or the Pediatric Review Equity Act and submitted to the FDA from September 1, 2007, to December 31, 2014, to support the approval of drugs frequently used for long-term therapy in children. Statistical analysis was performed from July 1, 2015, to December 31, 2017.

MAIN OUTCOMES AND MEASURES—Maximum duration of trials submitted to support FDA approval of drugs for children.

Corresponding Author: Kanecia O. Zimmerman, MD, MPH, Duke Clinical Research Institute, Duke University School of Medicine, PO Box 3352, Durham, NC 27710 (kanecia.obie@dm.duke.edu).

Author Contributions:

Dr Zimmerman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Zimmerman, Smith, McMahon, Murphy, McCune.

Acquisition, analysis, or interpretation of data: Zimmerman, Smith, Temeck, Avant, McCune. *Drafting of the manuscript:* Zimmerman, McMahon, Murphy.

Critical revision of the manuscript for important intellectual content: Smith, McMahon, Temeck, Avant, McCune.

Statistical analysis: Zimmerman.

Administrative, technical, or material support: Avant.

Supervision: Smith, McMahon, Temeck, Murphy, McCune.

Conflict of Interest Disclosures:

Dr Smith reported receiving compensation for serving as a consultant for Astellas Pharma, Lediant, and Nestec. No other disclosures were reported.

Disclaimer:

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the US Food and Drug Administration.

RESULTS—A total of 306 trials supporting 86 drugs intended for long-term use in children were eligible for the primary analysis. The drugs most commonly evaluated were for treatment of neurologic (25 [29%]), pulmonary (16 [19%]), and anti-infective (14 [16%]) indications. The median maximum trial duration by drug was 44 weeks (minimum, 1.1 week; maximum, 364 weeks). For nearly two-thirds of the drugs (52 [61%]), the maximum trial duration was less than 52 weeks. For 10 of the drugs (12%), the maximum trial duration was 3 years or more. Maximum duration of trials did not vary by therapeutic category, minimum age of enrollment, calendar year, or legislative mandate.

CONCLUSIONS AND RELEVANCE—Pediatric clinical trials designed to sufficiently investigate drug safety and efficacy to support FDA approval are of relatively limited duration. Given the potential long-term exposure of patients to these drugs, the clinical community should consider whether new approaches are needed to better understand the safety associated with long-term use of these drugs.

During the past 20 years, research has established marked differences between children and adults in drug pharmacokinetics and pharmacodynamics. If pharmacokinetics and pharmacodynamics are not adequately considered in pediatric dosing, ontogenesis of drug receptors and pathways of biotransformation can lead to therapeutic failure or drug toxic effects.[1–5]

Through mechanisms and incentives provided in the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), the US government recognizes the importance of studying drug safety and efficacy within pediatric populations.[1] These legislative acts have had notable success, resulting thus far in more than 700 changes in US Food and Drug Administration (FDA) product labels to include pediatric information.[6] However, the study of drugs within pediatric populations is complex. Chronic disease is becoming more prevalent among children and often requires lifelong drug therapy.[7–9] Furthermore, the administration of some drugs during vulnerable periods of growth and development may have implications for the attainment of adequate growth and development among children.[10–12] Given the potential for long-term administration of drugs to pediatric patients, drug safety may need to be assessed for prolonged durations and during vulnerable periods of growth and development.

We have limited understanding of the current state of long-term drug safety evaluations in children. To improve our understanding, we evaluated the duration of clinical trials submitted to the FDA under BPCA and PREA, with a focus on drugs potentially administered to children with chronic health conditions. We then reviewed the literature for other studies conducted for children or adults that could provide guidance for feasibility and alternative methods for gathering data on long-term drug administration in children. Such efforts are necessary first steps toward understanding the availability of data on long-term drug safety in children.

Methods

Data Sources and Inclusion Criteria

We used the FDA's Document Archiving, Reporting, and Regulatory Tracking System electronic database as our data source for clinical trial submissions to the agency. Within this database, we identified all drugs submitted to and reviewed by the FDA, under BPCA and PREA, for pediatric drug approval from September 1, 2007, to December 31, 2014. Drugs that did not receive FDA approval for the intended pediatric indication were excluded. We also excluded drugs administered topically (including administration to the skin, eye, or ear) unless previous evidence suggested substantial systemic absorption. We extracted deidentified data from prospective drug trials in humans as well as FDA medical, statistical, and pharmacokinetic reviews of the primary data. This research study did not require Research Involving Human Subjects Committee review and approval because it is exempt from the requirements of 45 CFR §46.101b(4).

A committee of 4 pediatricians (K.O.Z., A.W.M., J.T., and S.M.), each with clinical and regulatory experience, characterized the potential uses of the drugs as short-term, intermediate, or long-term, based on the typical or expected clinical use in pediatric populations. The safety and efficacy data sufficient for FDA approval of a drug for its intended length of use may not include data on longer-term use. The analysis described herein focused on the trial length for drugs potentially used for the long-term medical management of children, excluding trials whose primary objective was to evaluate bioequivalence, pharmacokinetics, or a device.

Our literature review included articles referenced in Medline and PubMed as of February 12, 2018. Search terms were limited to "safety" AND the generic or brand name for the specific drug of interest OR "long-term" AND "safety" AND the generic or brand name for the specific drug of interest.

Definitions and Outcomes

The committee defined *short-term therapy* as drugs typically administered for less than 3 months, *intermediate therapy* as drugs typically administered for 3 to 6 months, and *long-term therapy* as drugs typically administered for longer than 6 months. Drugs classified as long-term therapy were further classified as continuous or intermittent. Continuous drugs were those administered on a scheduled basis dependent on drug pharmacokinetics (ie, daily, weekly, or monthly), while intermittent drugs were those administered seasonally.

We classified drugs into the following therapeutic categories according to the primary indication or affected organ system: anti-infectives, biologics, cardiology, dermatology, endocrinology and metabolism, gastroenterology, hematology, neurology, pulmonology, and miscellaneous. The miscellaneous category included drugs for urologic indications (eg, overactive bladder) and those for ophthalmologic disease without anti-infective activity. We designated the following age groups according to the minimum age required for enrollment in each trial: infants (<1 year), children (1 to <9 years), preadolescents (9 to <12 years), and adolescents (12 to ≤17 years).

For our analysis, we identified all trials submitted as primary evidence for pediatric drug efficacy and safety. We defined trial duration as the sum of controlled and uncontrolled periods during which children received drug therapy. The entire duration of crossover trials and trials with cyclical drug administration, including interval periods of drug washout or time off therapy, was included. For each drug (unit of analysis), we identified the median maximum trial duration. We then compared the maximum trial duration with the study durations identified in our literature review and identified specific drugs and drug classes that might warrant further safety assessments based on available data.

Data Collection

We collected the following information regarding each drug trial: therapeutic area, indication, clinical trial design (eg, open-label uncontrolled, randomized controlled, or long-term extension), ages studied, duration of drug receipt (weeks), year of FDA evaluation, and legislation under which the study took place (ie, BPCA or PREA). In our literature review, we extracted information regarding patient population, type and duration of evaluation, and any noted safety concerns or calls for additional long-term data in children.

Statistical Analysis

Statistical analysis was performed from July 1, 2015, to December 31, 2017. We used standard summary statistics, including counts (with percentages) and medians (25th and 75th percentiles) to describe the study variables. We evaluated outcomes by therapeutic classification and age category, and made comparisons using a Wilcoxon rank sum test. Changes in trial duration by study year were evaluated using Kruskal-Wallis equality-of-populations rank test. We used STATA, version 14.1 (StataCorp) to perform all statistical analyses. All P values were from 2-sided tests and results were deemed statistically significant at $P < .05$.

Results

We identified 201 drugs submitted for pediatric labeling during the study period. Of these, we excluded 33 drugs that were not approved, 19 vaccines, 3 drugs used for imaging studies, and 19 topical drugs. Of the remaining 127 drugs, we identified 33 that would be used for short-term indications, 5 for intermediate-length indications, and 86 drugs potentially used for long-term therapy. Pharmacokinetic trials were submitted for only 3 drugs. A total of 306 trials supporting the 86 long-term therapy drugs were eligible for our analysis (eTable in the Supplement). Of the 86 drugs, 19 (22%) were characterized as long-term intermittent and 67 (78%) as long-term continuous (Figure 1).

A total of 25 (29%) of the 86 included drugs were for neurologic indications, 16 (19%) were for pulmonary indications, and 14 (16%) were for anti-infective indications (Table 1). Trials for nearly half of the drugs (40 [47%]) were conducted in response to BPCA alone or BPCA and PREA, and the remainder were in response to PREA alone. For 24 of the drugs (28%), the minimum age of enrollment in the trials was younger than 1 year. A total of 42 drugs (49%) had trials that initiated enrollment at ages 1 to 8 years, 7 (8%) initiated enrollment at ages 9 to 11 years, and 10 (12%) initiated enrollment at ages 12 to 17 years.

The median (25th and 75th percentiles) maximum trial duration by drug was 44 weeks (12 weeks and 53 weeks). For nearly two-thirds of the drugs (52 [61%]), the duration was less than 52 weeks (<1 year) (Table 2). The longest trial duration by drug (364 weeks/7 years) investigated the safety and efficacy of a phenyalanine hydroxylase activator for children with phenylketonuria, while the shortest duration (1.1 week) investigated the efficacy and safety of montelukast for the indication of exercise-induced asthma (longer studies were done for the other pediatric indications for montelukast).

Although trial duration appeared different between therapeutic categories, the overall distributions of trial durations were statistically similar because of the wide variability in the trial lengths. For example, the median (25th and 75th percentiles) maximum duration for biologic drug trials was 132 weeks (52 weeks and 260 weeks); for cardiovascular drugs, median maximum duration was 54 weeks (53 weeks and 57 weeks; $P = .44$) (Figure 2). Similarly, trial duration did not vary according to classification as a long-term intermittent or long-term continuous drug, with median (25th and 75th percentiles) maximum durations of 12 weeks (8 weeks and 52 weeks) for long-term intermittent drugs and 48 weeks (15 weeks and 58 weeks) for long-term continuous drugs ($P = .08$).

Overall distribution of trial duration varied inconsistently by indication within a therapeutic category. For example, within the neurology category, drugs with a primary indication for seizures had a median (25th and 75th percentiles) maximum trial duration (139.5 weeks [242 weeks and 291 weeks]) that was statistically significantly different from those with a nonseizure indication (29 weeks [8 weeks and 48 weeks]; $P = .04$). However, within the pulmonary category, drugs with a primary asthma indication had a similar median (25th and 75th percentiles) maximum trial duration (34 weeks [8 weeks and 52 weeks]) compared with those without such an indication (25 weeks [14 weeks and 52 weeks]; $P = .91$). The FDA labels for drugs denoted as long-term continuous were each labeled for “maintenance therapy” or “for treatment of” a specified chronic condition. Labels for long-term intermittent drugs most often had specified durations of short-term use consistent with durations of clinical trials submitted to support labeling for the specified drug.

Trials enrolling participants of minimum ages of 0 (infant), 1 (child), or 12 (adolescent) years all had similar median (25th and 75th percentiles) maximum durations (infant, 42 weeks [10 weeks and 59 weeks]; child, 50 weeks [16 weeks and 54 weeks]; and adolescent, 52 weeks [12 weeks and 53 weeks) (Figure 3). Median (25th and 75th percentiles) maximum trial duration did not vary according to whether the trial was mandated by BPCA and PREA (48 weeks [15 weeks and 100 weeks]) or PREA alone (29 weeks [10.7 weeks and 52 weeks]) ($P = .17$). Furthermore, trial duration did not change significantly over time: in 2007, the median (25th and 75th percentiles) maximum duration was 52 weeks (12 weeks and 54 weeks); in 2014, this duration was 39 weeks (25 weeks and 86 weeks) ($P = .70$). Approximately 35% of included drugs (30) had extension trials, most commonly occurring for neurologic drugs (14 of 25 [56%]). Only 3 of the 30 drugs (10%) with extension trials used a controlled study design.

According to our review of the literature, long-term evaluations exceeded the duration of trials submitted as primary evidence to the FDA for 69 (80%) of the 86 drugs. For 67 drugs

(78%),long-term evaluations included prospective studies, most often characterized as nonrandomized, open-label, observational studies with standardized follow-up evaluation. Children were included in evaluations for 37 (43%) of the drugs.

Several safety findings with potential long-term implications emerged from our literature review. First, although most studies did not identify substantial effects of inhaled cortico steroids on linear growth or the hypothalamic-pituitary-axis, investigators and clinicians remain concerned about this potential phenomenon and highlight a need for more prolonged evaluations, particularly at critical times of pediatric growth and development.[13–18] Second, proton pump inhibitors have been associated with gastric hyperplasia among those with long-term use, and existing evaluations in children are considered inadequate to rule out this adverse event.[19–21] Third, short-term and longer-term evaluations of stimulants have been associated with insomnia, concern for abnormal cognitive development, and impaired growth; quantification of risks are not fully elucidated.[22–24] Mood stabilizers and anti-psychotics have shown associations with weight gain and metabolic derangements, the long-term effects of which are unclear.[25–27]Omalixumab carries an FDA warning because heart and brain issues have not been ruled out with existing studies.[28] Finally, tenofovir may have implications for long-term renal function.[29–32] We did not identify substantial long-term safety concerns for other evaluated drugs or drug classes.

Discussion

In our analysis of data submitted to the FDA from 2007 to 2014 to support pediatric indications for drugs that are commonly used for chronic conditions, we found that the median maximum trial duration by drug infrequently exceeded 1 year. Furthermore, trial duration did not notably vary with therapeutic category, minimum age of enrollment, calendar year, or legislative mandate. Review of the literature suggests that longer-term data in nonrandomized, observational studies are available for many drugs and may provide potentially important information regarding safety signals.

Admittedly, our study is limited given its purely descriptive nature. We have categorized our data to facilitate analysis, but recognize that the available data are heterogeneous with respect to the drugs evaluated, indications for therapy, study populations, and disease processes. Such categorization does not allow for evaluation of more subtle differences between trials. Finally, we have characterized drugs as long-term intermittent or long-term continuous based on clinical experience and prior documentation of long-term use of drugs even in cases for which the labeled indication may not support such use (eg, proton pump inhibitors).[33] We therefore acknowledge that this classification introduces some bias in our analysis. Nonetheless, our study provides important baseline information that can inform discussion regarding long-term drug safety data in children.

Our findings suggest that these pediatric studies may not provide complete safety data across all critical periods of growth and development. This observation may be important because multiple periods of critical pediatric growth and development exist, including marked deceleration in linear growth and weight gain during the first 2 years of life, and initiation of puberty around ages 11 to 13 years, accompanied by acceleration in linear growth that may

last for 3 to 4 years.[34,35] Although the first 3 years of life are often considered more critical than older ages for brain development, biochemical studies of brain metabolism suggest that high brain metabolic rates characteristic of early childhood may not decline to adult levels until ages 16 to 18 years, suggesting that the school-age and adolescent periods are equally critical periods of brain development.[36] Given this information, even the longest trial duration identified in our study (364 weeks/7 years) does not completely evaluate potential critical stages of all pediatric growth and development periods, nor does it begin to characterize the exposure associated with lifelong therapy.[1]

Administration of dexamethasone to premature infants provides a pertinent example in which long-term follow-up after limited administration in the neonatal period revealed important information regarding drug safety associated with exposure during critical periods of cognitive development. Extensive investigation dating to 1990 identified dexamethasone as an effective therapy for facilitation of extubation and prevention of bronchopulmonary dysplasia in premature infants.[37] However, in long-term follow-up studies,[38] investigators identified a statistically significantly increased risk of cerebral palsy among infants who received dexamethasone, compared with those who did not, with a number needed to harm of 4. Examples such as this one underscore potential issues with limited long-term data on drug safety in children.

On average, more than 1 decade elapses between initial laboratory formulation of a drug to readiness for public use in adults.[39] Public availability of data on drug efficacy and safety in children may require an additional 6 years.[40] Requiring that studies be designed to cover all the potential periods of critical development would make pediatric drug development infeasible. Furthermore, although investigators have traditionally touted the controlled clinical trial as the most rigorous source of data, multiple barriers to the conduct of clinical trials exist and may be exacerbated when clinical trials are of prolonged duration.[41,42] A recent investigation of more than 500 clinical trials conducted for children found that nearly 20% were discontinued early, largely owing to poor patient accrural.[43] Previous investigators have long documented attrition rates as high as 15% in longitudinal pediatric studies and up to 44% in some interventional studies in specific pediatric populations.[44–46] Furthermore, the relatively small sample sizes of pediatric trials compared with adult trials, combined with the lack of a control group in many extension trials, may raise concern about the level of evidence for safety such trials can provide.[47,48] Innovative approaches to acquire information on long-term drug safety in children are needed that continue to make important therapeutics available to children in a timely manner.

Multiple approaches are likely needed to obtain high-quality, long-term safety data for drugs used to treat chronic pediatric conditions. Currently, the FDA evaluates need for long-term safety assessment based on any safety concerns related to the specific effects of the drugs, the intended duration of treatment, and potential exposure during critical periods of growth and development, despite lack of conclusive evidence that all drugs used long-term in children will have specific effects on growth and development. In addition, the Food and Drug Administration Amendments Act of 2007 required increased activities for active post marketing risk identification and analysis. More importantly, it may be possible to leverage safety information from other populations, including adults and other pediatric age groups.

Our review of the literature suggests that long-term data can take many forms, ranging from open-label extension trials[49–51] after randomized studies, to registries[52] that capture data for specific disease processes, or prospective longitudinal studies[53] designed to answer specific scientific questions. Furthermore, with increasing administration of drugs for chronic conditions such as attention-deficit/hyperactivity disorder and asthma, we have a ready source of real-world data from which to potentially evaluate longer-term safety.[54]

Although we were able to identify potentially important safety signals from different data sources in the literature, each source has benefits and limitations, and our search may have introduced bias due to the nature of our study question. In general, ability to use the data in a meaningful way hinges on collecting quality data from an adequate pediatric population. To this end, the following approaches may enhance data quality: 1) use of existing literature to highlight areas for more urgent evaluation and lessons learned about specific data sources for specific drugs/drug classes; 2) collaboration between stake-holders and formation of networks for large sample sizes and acquisition of protocol-directed data collection in prospective observational studies for specific safety signals; 3) investigation of methods to decrease attrition and improve data collection in extension phases of clinical trials or other prospective evaluations; and 4) application of rigorous pharmacoepidemiologic analysis methods to existing data sources (‘real-world data’) and naturally occurring cohorts (eg, clinical cohorts, members of disease registries). Concerted efforts among all stakeholders will enable us to continue to advance pediatric drug development with regard to long-term pediatric drug safety while maintaining efficient and timely access to approved therapies for all children.

Limitations

This study has some limitations. As mentioned above, our study is limited by its purely descriptive nature; the available data are heterogeneous with respect to the drugs evaluated, indications for therapy, study populations, and disease processes, which did not allow us to evaluate more subtle differences between trials. Also, our classification (long-term intermittent vs continuous) is based on experience, which may have introduced bias into our analyses.

Conclusions

Pediatric clinical trials that are designed to sufficiently investigate drug safety and efficacy to support FDA approval are of relatively limited duration. Given the potential long-term exposure of patients to these drugs, the clinical community should consider whether new approaches are needed to better understand the safety of long-term use of these drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support:

Dr Zimmerman is funded by grant KL2TR001115 from the Duke Clinical and Translational Science Awards and grant K23HD091398 from the Eunice Kennedy Shriver Institute of Child Health and Human Development (NICHD). Dr Smith receives salary support for research from grants NIH-1R21HD080606–01; U2COD023375 from the National Institutes of Health (NIH), grant UL1TR001117 from the National Center for Advancing Translational Sciences of the NIH, contract HHSN275201000003I from the NICHD, and grant 1R18-FD005292–01 from the US Food and Drug Administration.

Role of the Funder/Sponsor:

The funding sources were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157-1167. doi:10.1056/NEJMra035092 [PubMed: 13679531]
2. Allegaert K, Anderson BJ, Verbesselt R, et al. Tramadol disposition in the very young: an attempt to assess in vivo cytochrome P-450 2D6 activity. Br J Anaesth. 2005;95(2):231-239. doi:10.1093/bja/aei170 [PubMed: 15951326]
3. Ginsberg G, Hattis D, Sonawane B, et al. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci. 2002;66(2): 185-200. doi:10.1093/toxsci/66.2.185 [PubMed: 11896285]
4. Madabushi R, Cox DS, Hossain M, et al. Pharmacokinetic and pharmacodynamic basis for effective argatroban dosing in pediatrics. J Clin Pharmacol. 2011;51(1):19-28. doi:10.1177/0091270010365550 [PubMed: 20421511]
5. Mirochnick M, Capparelli E, Connor J. Pharmacokinetics of zidovudine in infants:a population analysis across studies. Clin Pharmacol Ther. 1999;66(1):16-24. doi:10.1016/S0009-9236(99)70049-4 [PubMed: 10430105]
6. Food US and Administration Drug. New pediatric labeling information database. https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase Accessed February 1, 2018.
7. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. JAMA. 2010;303(7):623-630. doi:10.1001/jama.2010.104 [PubMed: 20159870]
8. van der Lee JH, Mokkink LB, Grootenhuis MA, Heymans HS, Offringa M. Definitions and measurement of chronic health conditions in childhood: a systematic review. JAMA. 2007;297(24): 2741-2751. doi:10.1001/jama.297.24.2741 [PubMed: 17595275]
9. Benjamin DK Jr, Smith PB, Sun MJ, et al. Safety and transparency of pediatric drug trials. Arch Pediatr Adolesc Med. 2009;163(12):1080-1086. doi:10.1001/archpediatrics.2009.229 [PubMed: 19996043]
10. Carrim ZI, McKay L, Sidiki SS, Lavy TE. Early intervention for the ocular and neurodevelopmental sequelae of fetal valproate syndrome. J Paediatr Child Health. 2007;43(9):643-645. doi:10.1111/j.1440-1754.2007.01176.x [PubMed: 17688650]
11. Cheong JLY, Burnett AC, Lee KJ, et al.; Victorian Infant Collaborative Study Group. Association between postnatal dexamethasone for treatment of bronchopulmonary dysplasia and brain volumes at adolescence in infants born very preterm. J Pediatr. 2014;164(4):737-743. doi:10.1016/j.jpeds.2013.10.083 [PubMed: 24332820]
12. Essig S, Li Q, Chen Y, et al. Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia:a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2014;15(8):841-851. doi:10.1016/S1470-2045(14)70265-7 [PubMed: 24954778]
13. Gulliver T, Morton R, Eid N. Inhaled corticosteroids in children with asthma: pharmacologic determinants of safety and efficacy and other clinical considerations. Paediatr Drugs. 2007;9(3): 185-194. doi:10.2165/00148581-200709030-00007 [PubMed: 17523699]

14. Dahl R Systemic side effects of inhaled corticosteroids in patients with asthma. Respir Med. 2006;100(8):1307-1317. doi:10.1016/j.rmed.2005.11.020 [PubMed: 16412623]
15. Blaiss MS. Safety update regarding intranasal corticosteroids for the treatment of allergic rhinitis. Allergy Asthma Proc. 2011;32(6):413-418. doi:10.2500/aap.2011.32.3473 [PubMed: 22221434]
16. Skoner DP, Maspero J, Banerji D; Ciclesonide Pediatric Growth Study Group. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. Pediatrics. 2008;121(1):e1-e14. doi:10.1542/peds.2006-2206 [PubMed: 18070931]
17. Chervinsky P, Kunjibettu S, Miller DL, et al. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2007;99(1):69-76. doi:10.1016/S1081-1206(10)60624-2 [PubMed: 17650833]
18. O'Connor BJ, Kilfeather S, Cheung D, et al. Efficacy and safety of ciclesonide in patients with severe asthma: a 12-week, double-blind, randomized, parallel-group study with long-term (1-year) follow-up. Expert Opin Pharmacother. 2010;11(17):2791-2803. doi: 10.1517/14656566.2010.526603 [PubMed: 20958119]
19. Eslami L, Nasseri-Moghaddam S. Meta-analyses: does long-term PPI use increase the risk of gastric premalignant lesions? Arch Iran Med. 2013;16(8):449-458. [PubMed: 23906249]
20. Gibbons TE, Gold BD. The use of proton pump inhibitors in children: a comprehensive review. Paediatr Drugs. 2003;5(1):25-40. doi:10.2165/00128072-200305010-00003
21. Tolia V, Boyer K. Long-term proton pump inhibitor use in children: a retrospective review of safety. Dig Dis Sci. 2008;53(2):385-393. doi:10.1007/s10620-007-9880-7 [PubMed: 17676398]
22. Powell SG, Frydenberg M, Thomsen PH. The effects of long-term medication on growth in children and adolescents with ADHD: an observational study of a large cohort of real-life patients. Child Adolesc Psychiatry Ment Health. 2015;9:50. doi:10.1186/s13034-015-0082-3 [PubMed: 26516345]
23. Adler LA, Spencer T, McGough JJ, Jiang H, Muniz R. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. J Atten Disord. 2009;12(5): 449-459. doi:10.1177/1087054708320397 [PubMed: 19218542]
24. Soto PL, Wilcox KM, Zhou Y, et al. Long-term exposure to oral methylphenidate or dl-amphetamine mixture in peri-adolescent rhesus monkeys: effects on physiology, behavior, and dopamine system development [published correction appears in Neuropsychopharmacology. 2013;38(6):1141] Neuropsychopharmacology. 2012; 37(12):2566-2579. doi:10.1038/npp. 2012.119 [PubMed: 22805599]
25. McDonnell DP, Landry J, Detke HC. Long-term safety and efficacy of olanzapine long-acting injection in patients with schizophrenia or schizoaffective disorder: a 6-year, multinational, single-arm, open-label study. Int Clin Psychopharmacol. 2014;29(6):322-331. doi:10.1097/YIC. 0000000000000038 [PubMed: 24850228]
26. Briles JJ, Rosenberg DR, Brooks BA, Roberts MW, Diwadkar VA. Review of the safety of second-generation antipsychotics: are they really "atypically" safe for youth and adults? Prim Care Companion CNS Disord. 2012;14(3):PCC.11r01298. doi:10.4088/PCC.11r01298 [PubMed: 23106030]
27. Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. Eur Child Adolesc Psychiatry. 2007;16(2):104-120. doi:10.1007/s00787-006-0580-1 [PubMed: 17075688]
28. Food US and Administration Drug. FDA drug safety communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. https://www.fda.gov/Drugs/DrugSafety/ucm414911.htm Accessed February 1, 2018.
29. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci. 2015;60(5):1457-1464. doi:10.1007/s10620-014-3486-7 [PubMed: 25532501]
30. Giacomet V, Nannini P, Vigano A, et al. Long-term renal effects of tenofovir-disoproxil-fumarate in vertically HIV-infected children, adolescents, and young adults: a 132-month follow-up study. Clin Drug Investig. 2015;35(7): 419-426. doi:10.1007/s40261-015-0293-7

31. Milazzo L, Gervasoni C, Falvella FS, et al. Renal function in HIV/HBV co-infected and HBV mono-infected patients on a long-term treatment with tenofovir in real life setting. Clin Exp Pharmacol Physiol. 2017;44(2):191-196. doi:10.1111/1440-1681.12691 [PubMed: 27809359]
32. Squillace N, Ricci E, Quirino T, et al.; CISAI Study Group. Safety and tolerability of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in a real life setting: data from Surveillance Cohort Long-Term Toxicity Antiretrovirals/Antivirals (SCOLTA) project. PLoS One. 2017;12(6):e0179254. doi:10.1371/journal.pone.0179254 [PubMed: 28632758]
33. Blank ML, Parkin L. National study of off-label proton pump inhibitor use among New Zealand infants in the first year of life (2005–2012). J Pediatr Gastroenterol Nutr. 2017;65(2):179-184. doi: 10.1097/MPG.0000000000001596 [PubMed: 28403034]
34. Tanner J Foetus Into Man: Physical Growth from Conception to Maturity. London: Open Books; 1978.
35. Tanner JM, Whitehouse RH, Marshall WA, Carter BS. Prediction of adult height from height, bone age, and occurrence of menarche, at ages 4 to 16 with allowance for midparent height. Arch Dis Child. 1975;50(1):14-26. doi:10.1136/adc.50.1.14 [PubMed: 164838]
36. Chugani HT. A critical period of brain development: studies of cerebral glucose utilization with PET. Prev Med. 1998;27(2):184-188. doi:10.1006/pmed.1998.0274 [PubMed: 9578992]
37. Yeh TF, Torre JA, Rastogi A, Anyebuno MA, Pildes RS. Early postnatal dexamethasone therapy in premature infants with severe respiratory distress syndrome: a double-blind, controlled study. J Pediatr. 1990;117(2, pt 1):273-282. doi:10.1016/S0022-3476(05)80547-5 [PubMed: 2199642]
38. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. BMC Pediatr. 2001;1:1. doi:10.1186/1471-2431-1-1 [PubMed: 11248841]
39. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ. 2003;22(2): 151-185. doi:10.1016/S0167-6296(02)00126-1 [PubMed: 12606142]
40. Hudgins JD, Bacho MA, Olsen KL, Bourgeois FT. Pediatric drug information available at the time of new drug approvals: a cross-sectional analysis. Pharmacoepidemiol Drug Saf. 2018;27(2): 161-167. doi:10.1002/pds.4351 [PubMed: 29148107]
41. Walach H, Loef M. Using a matrix-analytical approach to synthesizing evidence solved incompatibility problem in the hierarchy of evidence. J Clin Epidemiol. 2015;68(11):1251-1260. doi:10.1016/j.jclinepi.2015.03.027 [PubMed: 26148834]
42. Fields MJ, Behrman RE, eds. Ethical Conduct of Clinical Research Involving Children. Washington, DC: National Academies Press; 2004.
43. Pica N, Bourgeois F. Discontinuation and nonpublication of randomized clinical trials conducted in children. Pediatrics. 2016;138(3): e20160223. doi:10.1542/peds.2016-0223 [PubMed: 27492817]
44. Aylward GP, Hatcher RP, Stripp B, Gustafson NF, Leavitt LA. Who goes and who stays: subject loss in a multicenter, longitudinal follow-up study. J Dev Behav Pediatr. 1985;6(1):3-8. doi: 10.1097/00004703-198502000-00003 [PubMed: 3882762]
45. Dias L, Schoenfeld E, Thomas J, et al.; COMET Group. Reasons for high retention in pediatric clinical trials: comparison of participant and staff responses in the Correction of Myopia Evaluation Trial. Clin Trials. 2005;2(5):443-452. doi:10.1191/1740774505cn113oa [PubMed: 16317812]
46. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer. 2013;119(5):1098-1105. doi: 10.1002/cncr.27854 [PubMed: 23132290]
47. Wainwright P Consent to open label extension studies: some ethical issues. J Med Ethics. 2002; 28(6):373-376. doi:10.1136/jme.28.6.373 [PubMed: 12468657]
48. Taylor GJ, Wainwright P. Open label extension studies: research or marketing? BMJ. 2005;331 (7516):572-574. doi:10.1136/bmj.331.7516.572 [PubMed: 16150772]
49. Pasi KJ, Fischer K, Ragni M, et al. Long-term safety and efficacy of extended-interval prophylaxis with recombinant factor IX Fc fusion protein (rFIXFc) in subjects with haemophilia B. Thromb Haemost. 2017;117(3):508-518. doi:10.1160/TH16-05-0398 [PubMed: 28004057]

50. Ozelo M, Misgav M, Abdul Karim F, et al. Long-term patterns of safety and efficacy of bleeding prophylaxis with turoctocog alfa (NovoEight) in previously treated patients with severe haemophilia A: interim results of the Guardian 2 extension trial. Haemophilia. 2015;21(5): e436-e439. doi:10.1111/hae.12737 [PubMed: 26058730]

51. Brunner G, Athmann C, Schneider A. Long-term, open-label trial: safety and efficacy of continuous maintenance treatment with pantoprazole for up to 15 years in severe acid-peptic disease. Aliment Pharmacol Ther. 2012;36(1):37-47. doi:10.1111/j.1365-2036.2012.05106.x [PubMed: 22531114]

52. Klotsche J, Niewerth M, Haas JP, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5): 855-861. doi:10.1136/annrheumdis-annrheumdis-2014-206747 [PubMed: 25926155]

53. Valério de Azevedo S, Maltez C, Lopes AI. Pediatric Crohn's disease, iron deficiency anemia and intravenous iron treatment: a follow-up study. Scand J Gastroenterol. 2017;52(1):29-33. doi: 10.1080/00365521.2016.1224381 [PubMed: 27576956]

54. Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D. Trends of outpatient prescription drug utilization in US children, 2002–2010. Pediatrics. 2012;130(1):23-31. doi: 10.1542/peds.2011-2879 [PubMed: 22711728]

Key Points

Question

What are the durations of pediatric clinical trials recently submitted to the US Food and Drug Administration, and how can this knowledge inform discussions of safety pharmacovigilance follow-up for drugs that might be used for long-term therapy in the pediatric population?

Findings

This study found that nearly two-thirds of pediatric clinical trials submitted to support the approval of drugs with potential long-term use in the pediatric population are shorter than 52 weeks.

Meaning

Pediatric clinical trials that are sufficient to support US Food and Drug Administration drug approval may require additional strategies to ensure data availability for understanding long-term drug safety in children.

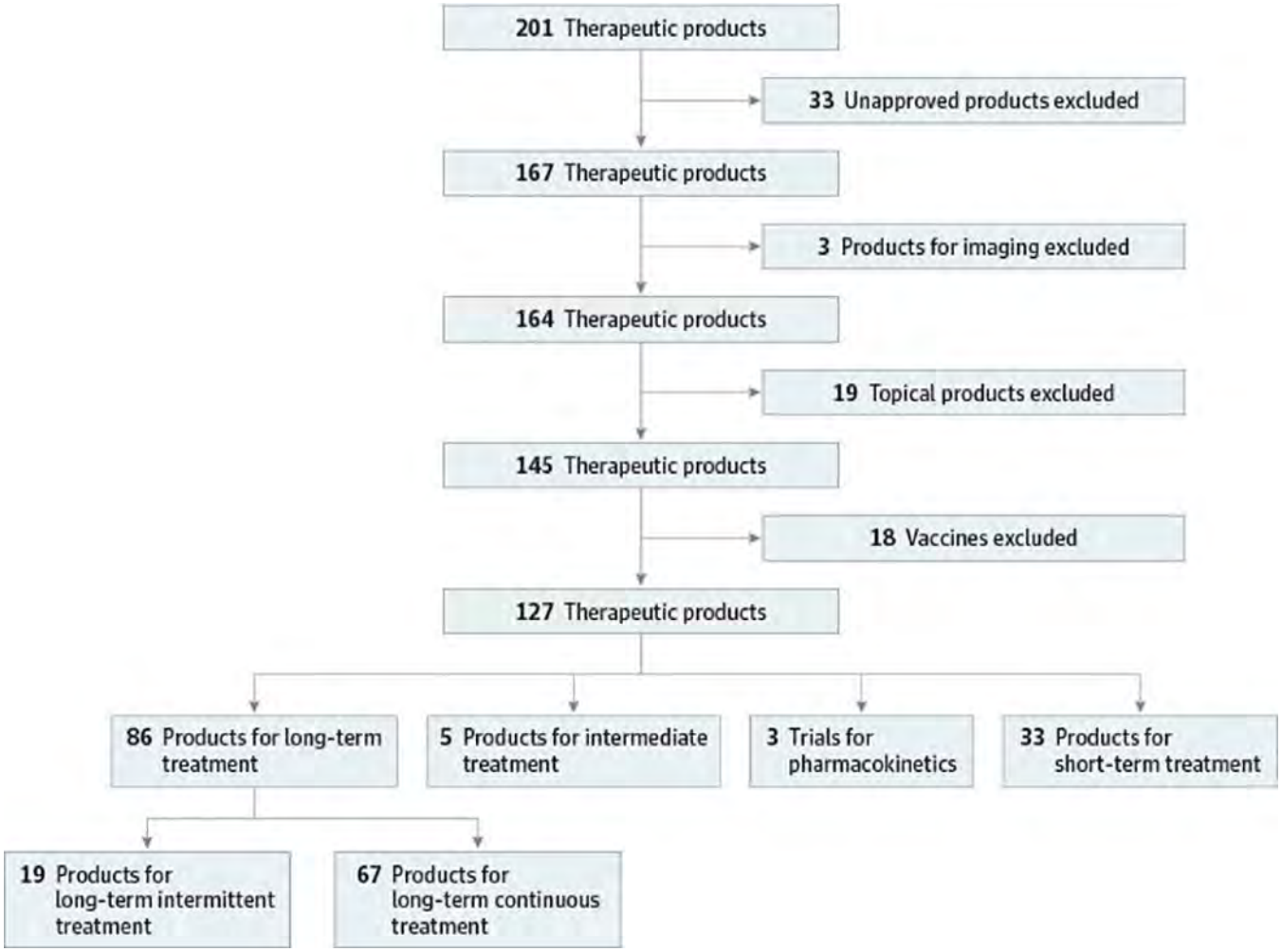


Figure 1.
CONSORT Diagram

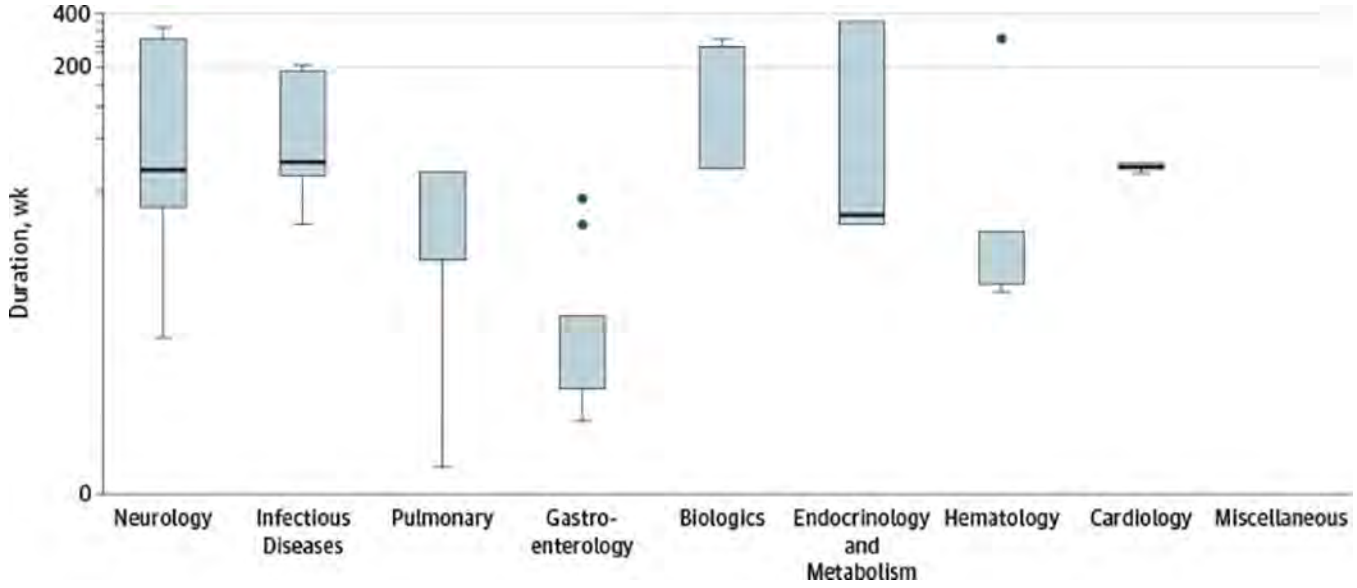


Figure 2. Maximum Trial Duration by Therapeutic Category

The black lines represent the median duration per therapeutic category. Upper and lower bounds of the box represent the 75th (quartile 3 [Q3]) and 25th (quartile 1 [Q1]) percentiles, respectively. The whiskers represent the following values:Q3 + 1.5(Q3 − Q1) andQ1 − 1.5(Q3 − Q1). Outliers within each therapeutic category are denoted by circles.

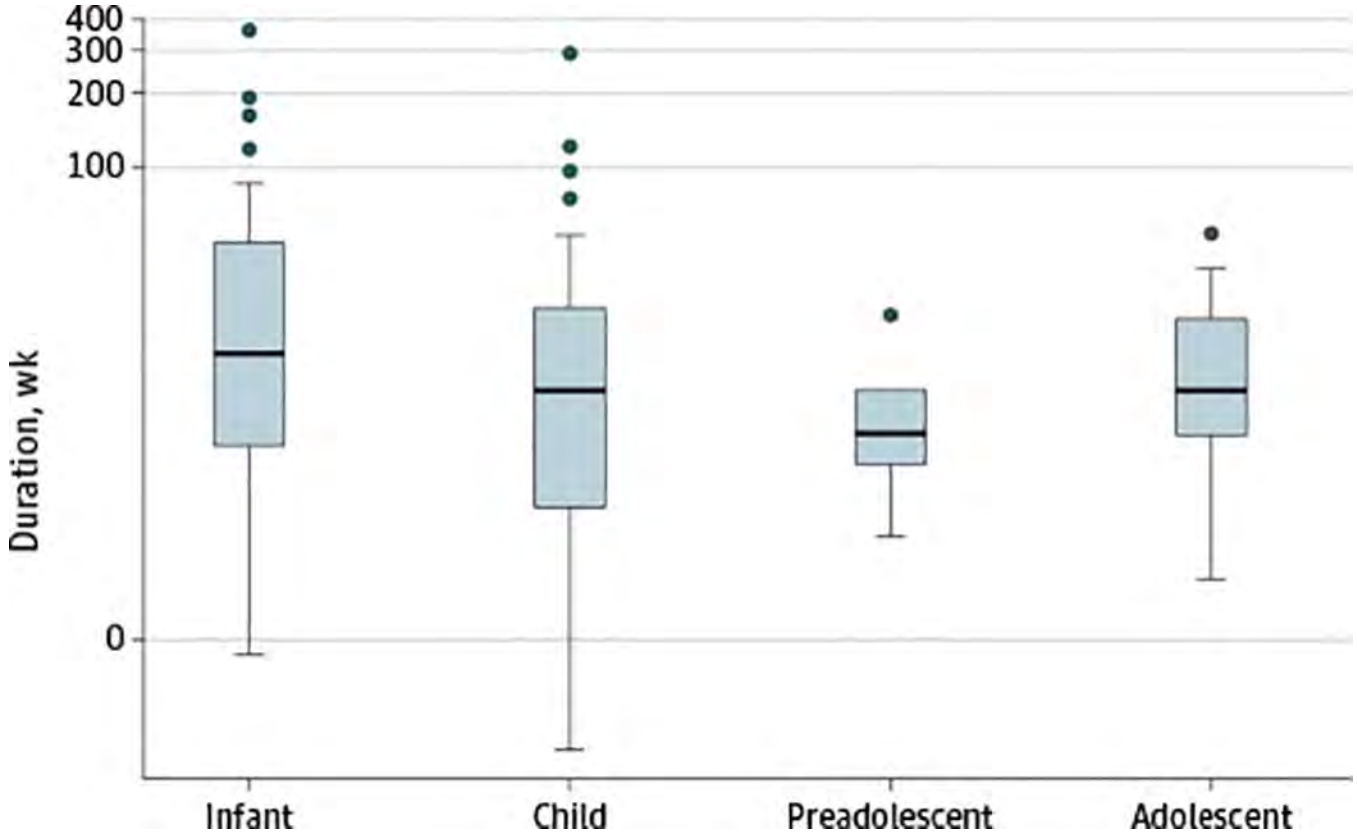


Figure 3. Maximum Trial Duration by Age Category

The black lines represent the median duration per age group. Upper and lower bounds of the box represent the 75th (quartile 3 [Q3]) and 25th (quartile 1 [Q1]) percentiles, respectively. The whiskers represent the following values:Q3 + 1.5(Q3 − Q1) and Q1 − 1.5(Q3 − Q1). Outliers within age group category are denoted by circles.

Table 1.

Drugs Used for Long-term Therapy and Supporting Trials by Therapeutic Category

	Drugs, No. (%)		
Category	**Overall (N = 86)**	**With Extension Trials (n = 30)**	**Trials, No. (%) (N = 306)**
Neurology	25 (29)	14 (47)	109 (35.6)
Pulmonary	16 (19)	3 (10)	91 (29.7)
Infectious diseases	14 (16)	3 (10)	35 (11.4)
Gastrointestinal	10 (12)	0	26 (8.5)
Biologic	6(7)	4(13)	20 (6.5)
Cardiology	5 (6)	5(17)	8 (2.6)
Hematology	5 (6)	0	6 (2.0)
Endocrine	4(5)	1(3)	6 (2.0)
Miscellaneous	1 (1)	0	5 (1.6)
Dermatology	0	0	0

Table 2.

Percentage of Drugs by Maximum Trial Duration for Long-term Therapeutics

	Drugs, No. (%)		
Maximum Trial Duration, Median, wk	**Total (N = 86)**	**Long-term Intermittent (n = 19)**	**Long-term Continuous (n = 67)**
<52	**52 (61)**	**13 (68)**	**39 (58)**
≥52 to <104	**21 (24)**	**5(26)**	**16 (24)**
≥104 to<156	**3(4)**	**0**	**3(5)**
≥156 to <208	**2(2)**	**0**	**2 (3)**
≥208 to <260	**2 (2)**	**0**	**2 (3)**
≥260	**6 (7)**	**1(5)**	**5 (8)**

Footnote 13

ICAN
Informed Consent Action Network

VIA FEDEX

October 12, 2017

U.S. Department of Health & Human Services
HHS Office of the Secretary
Eric D. Hargan
Acting Secretary of Health & Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *HHS Vaccine Safety Responsibilities and Notice Pursuant to 42 U.S.C. § 300aa-31*

Dear Secretary Hargan:

Informed Consent Action Network hereby provides notice per 42 U.S.C. § 300aa-31(b).

Americans, including the over 55 organizations listed below, whose members exceed 5 million Americans, are concerned about vaccine safety. The National Childhood Vaccine Injury Act of 1986 (the **1986 Act**) made nearly every aspect of vaccine safety the exclusive responsibility of the Department of Health & Human Services (**HHS**). As the Secretary of HHS (the **Secretary**), this means you shoulder virtually all responsibility for assuring the safety of vaccines administered to America's 78 million children.

This notice respectfully requests confirmation that certain obligations regarding vaccine safety required under the 1986 Act have been fulfilled or will forthwith be fulfilled. These specific requests are numbered sequentially in this notice. We would welcome the opportunity to meet and discuss reasonable means for complying with these requests. If that is not possible, the 1986 Act authorizes "a civil action … against the Secretary where there is alleged a failure of the Secretary to perform any act or duty" under the 1986 Act.

I. Background

The 1986 Act granted economic immunity to pharmaceutical companies for injuries caused by their vaccines. (42 U.S.C. § 300aa-11.) The 1986 Act thereby eliminated the market force which drives safety for all other products – actual and potential product liability. Recognizing the unprecedented elimination of this market force, the 1986 Act makes HHS directly responsible for virtually every aspect of vaccine safety. (42 U.S.C. §§ 300aa-2, 300aa-27.)

When the CDC recommends a pediatric vaccine for universal use, it creates for that vaccine's maker a liability free market of 78 million children typically required by law to receive the vaccine. The number of required vaccines has grown rapidly since 1986. In 1983, the CDC recommended that babies under one receive two vaccines: DTP and Polio.[1] As of 2017, the CDC recommends that babies under one receive multiple doses of ten vaccines: DTaP, Polio, Hep B, Rotavirus, Hib, Pneumococcal, Influenza, MMR, Varicella, and Hep A.[2] In total, the current CDC childhood vaccine schedule includes 56 injections of 73 doses of 30 different vaccines.

II. Deficiencies in the Pre-Licensure Safety Review of Pediatric Vaccines

All drugs licensed by the FDA undergo long-term double-blind pre-licensure clinical trials during which the rate of adverse reactions in the group receiving the drug under review is compared to the rate of adverse reactions in a group receiving an inert placebo, such as a sugar pill or saline injection. For example: Enbrel's pre-licensure trials followed subjects up to 80 months and controls received a saline injection.[3] Lipitor's pre-licensure trials lasted a median of 4.8 years and controls received a sugar pill.[4] Botox's pre-licensure trials lasted a median of 51 weeks and controls received a saline injection.[5] And even with these long-term studies, drugs are still often recalled.

In contrast, vaccines are *not* required to undergo long-term double-blind inert-placebo controlled trials to assess safety. In fact, not a single one of the clinical trials for vaccines given to babies and toddlers had a control group receiving an inert placebo. Further, most pediatric vaccines currently on the market have been approved based on studies with inadequate follow-up periods of only a few days or weeks.

For example, of the two Hepatitis B vaccines licensed by the FDA for injection into one-day-old babies, Merck's was licensed after trials that solicited adverse reactions for *only five days* after vaccination and GlaxoSmithKline's was licensed after trials that solicited adverse reactions for *only four days* after vaccination.[6] Similarly, the HiB vaccines sold by these same companies were licensed based on trials which solicited adverse reactions for three and four days, respectively, after vaccination.[7] The only stand-alone polio vaccine was licensed after a mere 48-hour follow-up period.[8]

---

[1] https://www.cdc.gov/vaccines/schedules/images/schedule1983s.jpg
[2] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf
[4] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf
[5] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf
[6] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf
[7] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM253652.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM179530.pdf
[8] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM133479.pdf

Moreover, these trials either had no control group or a control group which received other vaccines as a "placebo."[9] This means each new vaccine need only be roughly as safe as one (or in some cases numerous) previously licensed vaccines. Such flawed and unscientific study designs cannot establish the actual safety profile of any vaccine. The real adverse event rate for a vaccine can only be determined by comparing subjects receiving the vaccine with those receiving an inert placebo. Yet, this basic study design, required for every drug, is not required before or after licensing a vaccine.

The 1986 Act expressly requires that you, as the Secretary, "shall make or assure improvements in … the licensing … and research on vaccines, in order to reduce the risks of adverse reactions to vaccines." (42 U.S.C. § 300aa-27(a)(2).) Given this statutory obligation:

(1) Please explain how HHS justifies licensing any pediatric vaccine without first conducting a long-term clinical trial in which the rate of adverse reactions is compared between the subject group and a control group receiving an inert placebo?

(2) Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life?

III. Post-Licensure Surveillance of Vaccine Adverse Events

The lack of pre-licensure safety data leaves the assessment of vaccine safety to the post-licensing period when they are being administered to children in the "real world." To capture vaccine adverse events in the real world, the 1986 Act established the Vaccine Adverse Events Reporting System (**VAERS**) operated by HHS. (42 U.S.C. § 300aa-25.)

In 2016, VAERS received 59,117 reports of adverse vaccine events, including 432 deaths, 1,091 permanent disabilities, 4,132 hospitalizations, and 10,284 emergency room visits.[10]

However, only a tiny fraction of adverse vaccine events are reported to VAERS. An HHS-funded study by Harvard Medical School tracked reporting to VAERS over a three-year period at Harvard Pilgrim Health Care involving 715,000 patients and found that "fewer than 1% of vaccine adverse events are reported."[11] A U.S. House Report similarly stated: "Former FDA Commissioner David A. Kessler has estimated that VAERS reports currently represent only a fraction of the serious adverse events."[12]

[9] Ibid.
[10] https://wonder.cdc.gov/vaers.html
[11] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[12] https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf

Assuming VAERS captures a full 1 percent of adverse events – which is more than is estimated – the VAERS data above from 2016 may reflect that in that year alone there were 5,911,700 adverse vaccine events, including 43,200 deaths, 109,100 permanent disabilities, 413,200 hospitalizations, and 1,028,400 emergency room visits.

Of course, these figures are merely estimates. It would be far better if adverse events reports were automatically created and submitted to VAERS to avoid the issue of underreporting. Automated reporting would provide invaluable information that could clarify which vaccines might cause which harms and to whom, potentially avoiding these injuries and deaths.

The idea of automating adverse reaction reporting to VAERS is not new or even difficult to achieve.[13] An agency within HHS, the Agency for Healthcare Research and Quality, sought to do exactly that in 2007 when it provided an approximately $1 million grant to automate VAERS reporting at Harvard Pilgrim Health Care.[14] The result was the successful automation of adverse event reports at Harvard Pilgrim:

> *Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions … were identified.*[15]

These results should have been concerning to HHS since they show that over only a three-year period, there were 35,570 reportable reactions in just 376,452 vaccine recipients.

After automating adverse events reports at Harvard Pilgrim, the developers of this system asked the CDC to take the final step of linking VAERS with the Harvard Pilgrim system so that these reports could be automatically transmitted into VAERS. Instead, the CDC refused to cooperate. As the Harvard grant recipients explained:

> *Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.*[16]

After three years and spending $1 million of taxpayers' money, the CDC refused to even communicate with the HHS' Harvard Medical School grant recipients. Given HHS's statutory mandate to assure safer vaccines, it should have rushed forward with automating VAERS reporting -- not ignored the requests by the HHS's Harvard grant recipients.

---

[13] https://healthit.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system
[14] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[15] Ibid.
[16] Ibid.

While HHS strongly supports automating public health surveillance systems, when it comes to vaccine safety, the CDC has only supported projects that would limit VAERS to passive surveillance.[17] Automation would improve safety and address many of the long-standing issues and limitations raised by CDC regarding VAERS.[18] Capturing "fewer than 1% of vaccine adverse events" thirty years after the passage of the 1986 Act is unacceptable -- and potentially deadly.

The 1986 Act expressly provides that you, as the Secretary, "shall make or assure improvements in … adverse reaction reporting … in order to reduce the risks of adverse reactions to vaccines." (42 U.S.C. § 300aa-27(a)(2).) Given this statutory obligation:

(3) Please explain why HHS failed to cooperate with Harvard to automate VAERS reporting? And detail any steps that HHS has taken since toward automating VAERS reporting?

(4) Please explain any specific steps taken by HHS to improve adverse reaction reporting to VAERS?

IV. Identifying What Injuries Are Caused by Vaccines

The first step in assuring safer vaccines is to identify what harms they cause. This would normally be accomplished pre-licensure by long-term, inert-placebo controlled trials – but these are never performed for vaccines. As for post-licensure monitoring, HHS has refused to improve VAERS as discussed above. Hence, assessing which vaccines cause which injuries is mainly left to post-licensure studies. HHS, unfortunately, has neglected to perform these studies.

In 1991, the Institute of Medicine (**IOM**) examined 22 commonly reported serious injuries following the DTP vaccine.[19] The IOM concluded the scientific literature supported a causal relationship between the DTP vaccine and 6 of these injuries: acute encephalopathy, chronic arthritis, acute arthritis, shock and unusual shock-like state, anaphylaxis, and protracted inconsolable crying.[20] The IOM, however, found the scientific literature was insufficient to conclude whether or not the DTP vaccine can cause 12 other serious injuries:

> *Aseptic meningitis; Chronic neurologic damage; Learning disabilities and attention-deficit disorder; Hemolytic anemia; Juvenile diabetes; Guillain-Barre syndrome; Erythema multiforme; Autism; Peripheral mononeuropathy; Radiculoneuritis and other neuropathies; Thrombocytopenia; Thrombocytopenic purpura*[21]

---

[17] http://www.ajpmonline.org/article/S0749-3797(12)00249-8/pdf; https://www.ncbi.nlm.nih.gov/pubmed/26209838; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/

[18] Ibid.

[19] https://www.nap.edu/read/1815/chapter/2#7

[20] Ibid.

[21] Ibid.

The IOM lamented that it "encountered many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines" and on the poor design of the few existing studies.[22] It therefore cautioned that: "If research capacity and accomplishment in this field are not improved, future reviews of vaccine safety will be similarly handicapped."[23]

In 1994, the IOM issued another report which examined the scientific literature for evidence that could either prove or disprove a causal link between 54 commonly reported serious injuries and vaccination for diphtheria, tetanus, measles, mumps, polio, hepatitis B, and Hib.[24] The IOM located sufficient science to support a causal connection between these vaccines and 12 injuries, including death, anaphylaxis, thrombocytopenia, and Guillain-Barre syndrome.[25] The IOM, however, found the scientific literature was insufficient to conclude whether or not these vaccines caused 38 other commonly reported serious injuries, including:

> *Demyelinating diseases of the central nervous system, Sterility, Arthritis, Neuropathy, Residual seizure disorder, Transverse myelitis, Sensorineural deafness, Optic neuritis, Aseptic meningitis, Insulin-dependent diabetes mellitus, SIDS*[26]

As in 1991, this IOM Report again stated, "The lack of adequate data regarding many of the adverse events under study was of major concern to the committee. Presentations at public meetings indicated that many parents and physicians share this concern."[27]

In 2011, more than fifteen years after the IOM Reports in 1991 and 1994, HHS paid the IOM to conduct another assessment regarding vaccine safety.[28] This third IOM Report reviewed the available science with regard to the 158 most common vaccine injuries claimed to have occurred from vaccination for varicella, hepatitis B, tetanus, measles, mumps, and rubella.[29] The IOM located science which "convincingly supports a causal relationship" with 14 of these injuries, including pneumonia, meningitis, hepatitis, MIBE, febrile seizures, and anaphylaxis.[30] The review found sufficient evidence to support "acceptance of a causal relationship" with 4 additional serious injuries.[31]

The IOM, however, found the scientific literature was insufficient to conclude whether or not those vaccines caused 135 other serious injuries commonly reported after their administration, including:

---

[22] https://www.nap.edu/read/1815/chapter/2#8
[23] https://www.nap.edu/read/1815/chapter/9
[24] https://www.nap.edu/read/2138/chapter/2#12
[25] https://www.nap.edu/read/2138/chapter/2#12
[26] Ibid.
[27] https://www.nap.edu/read/2138/chapter/12
[28] https://www.nap.edu/read/13164/chapter/2#2
[29] Ibid.
[30] https://www.nap.edu/read/13164/chapter/2#3
[31] Ibid.

Encephalitis, Encephalopathy, Infantile Spasms, Afebrile Seizures, Seizures, Cerebellar Ataxia, Acute Disseminated Encephalomyelitis, Transverse Myelitis, Optic Neuritis, Neuromyelitis Optica, Multiple Sclerosis, Guillain-Barre Syndrome, Chronic Inflammatory Demyelinating Polyneuropathy, Brachial Neuritis, Amyotrophic Lateral Sclerosis, Small Fiber Neuropathy, Chronic Urticaria, Erythema Nodosum, Systemic Lupus Erythematosus, Polyarteritis Nodosa, Psoriatic Arthritis, Reactive Arthritis, Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Arthralgia, Autoimmune Hepatitis, Stroke, Chronic Headache, Fibromyalgia, Sudden Infant Death Syndrome, Hearing Loss, Thrombocytopenia, Immune Thrombocytopenic Purpura[32]

Thus, out of the 158 most common serious injuries reported to have been caused by the vaccines under review, the evidence supported a causal relationship for 18 of them, rejected a causal relationship for 5 of them, but for the remaining 135 vaccine-injury pairs, over 86 percent of those reviewed, the IOM found that the science simply had not been performed.[33]

The 1986 Act expressly provides that you, as the Secretary, "shall promote the development of childhood vaccines that result in fewer and less adverse reactions" and "shall make or assure improvements in … the … labeling, warning, … and research on vaccines, in order to reduce the risks of adverse reactions to vaccines." (42 U.S.C. § 300aa-27(a)(2).) The first step in reducing adverse reactions is identifying what adverse reactions are caused by vaccine. Given this statutory obligation:

(5) For each of the 38 vaccine-injury pairs reviewed in the 1994 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

(6) For each of the 135 vaccine-injury pairs reviewed in the 2011 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Further to your duties to identify what injuries are caused by vaccines, the 1986 Act also expressly requires you to "make or assure improvements in … the … recall of reactogenic lots or batches, of vaccines … in order to reduce the risks of adverse reactions to vaccines" and thus each "health care provider who administers a vaccine … shall record … in such person's permanent

[32] Ibid.

[33] Ibid.

medical record … the vaccine manufacturer and lot number." (42 U.S.C. §§ 300aa-25(a), 300aa-27(a)(2).) Since health care providers often fail to record this information:

> **(7) Please explain what HHS has done to assure that health care providers record the manufacturer and lot number for each vaccine they administer?**

V. Identifying Which Children are Susceptible to Vaccine Injury

The IOM has consistently acknowledged there is individual susceptibility to serious vaccine injuries. The IOM has also acknowledged that research on such susceptibility must be done on an individual basis, considering a child's personal genome, behaviors, microbiome, intercurrent illness, and present and past environmental exposure. HHS, unfortunately, has not conducted this research.

In 1994, the IOM, building on concerns raised in its 1991 report, stated: "The committee was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not."[34] The IOM urged that "research should be encouraged to elucidate the factors that put certain people at risk."[35]

Yet, seventeen years later, in 2011, the IOM acknowledged this research had still not been done:

> *Both epidemiologic and mechanistic research suggest that most individuals who experience an adverse reaction to vaccines have a preexisting susceptibility. These predispositions can exist for a number of reasons—genetic variants (in human or microbiome DNA), environmental exposures, behaviors, intervening illness, or developmental stage, to name just a few—all of which can interact…*
>
> *Some of these adverse reactions are specific to the particular vaccine, while others may not be. Some of these predispositions may be detectable prior to the administration of vaccine… much work remains to be done to elucidate and to develop strategies to document the immunologic mechanisms that lead to adverse effects in individual patients.* [36]

In 2013, HHS commissioned the IOM to review the safety of the entire vaccine schedule.[37] The IOM again explained that while "most children who experience an adverse reaction to immunization have preexisting susceptibility," the IOM:

---

[34] https://www.nap.edu/read/2138/chapter/12#307. *See also* https://www.nap.edu/read/1815/chapter/9

[35] Ibid.

[36] https://www.nap.edu/read/13164/chapter/5#82

[37] https://www.nap.edu/read/13563/chapter/1

> *found that evidence assessing outcomes in sub populations of children who may be potentially susceptible to adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited and is characterized by uncertainty about the definition of populations of interest and definitions of exposures and outcomes*.[38]

HHS had failed to even define the terminology for the study of susceptible subpopulations and hence IOM admonished HHS to "develop a framework that clarifies and standardizes definitions of … populations that are potentially susceptible to adverse events."[39]

The IOM correctly points out in 2011 that given the "widespread use of vaccines" and "state mandates requiring vaccination of children … it is essential that safety concerns receive assiduous attention."[40] This is the same call for diligent attention that the IOM made in 1991 and 1994. Unfortunately, all of these calls for action have gone unheeded. The critical scientific inquiry to identify individuals susceptible to serious vaccine injury has never been conducted.

The 1986 Act expressly provides that you, as the Secretary, "shall promote the development of childhood vaccines that result in fewer and less adverse reactions" and "shall make or assure improvements in … the … labeling, warning, … and research on vaccines, in order to reduce the risks of adverse reactions to vaccines." (42 U.S.C. § 300aa-27(a)(2).) Given this statutory obligation:

> **(8) Please advise when HHS intends to begin conducting research to identify which children are susceptible to serious vaccine injury? If HHS believes it has commenced this research, please detail its activities regarding same?**

VI. Removing Claim "Vaccines Do Not Cause Autism" from the CDC Website

HHS, unfortunately, has treated vaccine safety as a public relations issue rather than a public health imperative. For example, the CDC claims on its website that "Vaccines Do Not Cause Autism" even though this broad claim is plainly not supported by the scientific literature.[41]

Indeed, as part of the IOM's 2011 review of vaccine safety, it was asked by HHS whether there is a causal relationship between autism and the DTaP vaccine administered to children at two, four, six, and fifteen months of age.[42] The IOM could not locate a single study supporting

[38] https://www.nap.edu/read/13563/chapter/9#130
[39] Ibid.
[40] https://www.nap.edu/read/13164/chapter/3#28
[41] https://www.cdc.gov/vaccinesafety/concerns/autism.html
[42] https://www.nap.edu/read/13164/chapter/2#2

that DTaP does not cause autism.[43] The IOM therefore concluded: "The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism."[44] The IOM's full explanation in its 2011 Report for this finding is attached as Appendix B. In fact, the only study the IOM could locate regarding whether DTaP causes autism, (Geier and Geier, 2004), concluded there *was* an association between DTaP and autism.[45] No research has been published since 2011 that could change the IOM's conclusion. Based on the foregoing, the CDC cannot validly make the blanket assertion that there is no causal relationship between vaccines and autism. The CDC nonetheless claims on its website that "Vaccines Do Not Cause Autism."

As with DTaP, there are also no published studies showing that autism is not caused by Hepatitis B, Rotavirus, Hib, Pneumococcal, Inactivated Poliovirus, Influenza, Varicella, or Hepatitis A vaccines – all of which HHS recommends babies receive, typically multiple times, by one year of age.[46]

Instead, HHS's claim that "Vaccines Do Not Cause Autism" relies almost entirely upon studies exclusively studying only one vaccine, MMR (which is administered no earlier than one year of age), or only one vaccine ingredient, thimerosal, with regard to autism.[47] Putting aside the controversy surrounding these studies, studies which focus on only one vaccine and one ingredient while ignoring the entire balance of the CDC's pediatric vaccine schedule cannot support the CDC's overarching declaration that "Vaccines Do Not Cause Autism."

As for the MMR vaccine, the CDC's own Senior Scientist, Dr. William Thompson[48], recently provided a statement through his attorney that the CDC "omitted statistically significant information" showing an association between the MMR vaccine and autism in the first and only MMR-autism study ever conducted by the CDC with American children.[49] Dr. Thompson, in a recorded phone call, stated the following regarding concealing this association: "Oh my God, I can't believe we did what we did. But we did. It's all there. It's all there. I have handwritten notes."[50] Dr. Thompson further stated on that call:

> *I have great shame now when I meet families with kids with autism because I have been part of the problem … the CDC is so paralyzed right now by anything related to autism. They're not doing what they should be doing because they're afraid to look for things that might be associated. So anyway*

[43] https://www.nap.edu/read/13164/chapter/12#545
[44] Ibid.
[45] Ibid. Ironically, this study was disregarded "because it provided data from a passive surveillance system [VAERS] and lacked an unvaccinated comparison population," which would be true of any study using VAERS data.
[46] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent. html
[47] https://www.cdc.gov/vaccinesafety/concerns/autism.html
[48] Dr. Thompson has been a scientist at CDC for nearly two generations and a senior scientist on over a dozen CDC publications at the core of many of CDC's vaccine safety claims. https://www.ncbi.nlm.nih.gov/pubmed
[49] http://www.rescuepost.com/files/william-thompson-statement-27-august-2014-3.pdf
[50] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio

> *there's still a lot of shame with that. … I am completely ashamed of what I did.*[51]

Hence, as for the only vaccine, MMR, actually studied by the CDC with regard to autism, it appears the CDC may have concealed an association between that vaccine and autism.[52]

When the former Director of the National Institute of Health, Dr. Bernadine Healy, was asked about whether public health authorities are correct to claim that vaccines do not cause autism, she answered: "You *can't* say that."[53] When asked again, Dr. Healy explained: "The more you delve into it – if you look at the basic science – if you look at the research that's been done, in animals – if you also look at some of these individual cases – *and*, if you look at the evidence that there *is* no link - what I come away with is: *The question has not been answered.*"[54]

Former NIH Director Dr. Healy goes on to explain:

> *This is the time when we do have the opportunity to understand whether or not there are susceptible children, perhaps genetically, perhaps they have a metabolic issue, mitochondrial disorder, immunological issue, that makes them more susceptible to vaccines plural, or to one particular vaccine, or to a component of vaccine... I haven't seen major studies that focus on - three hundred kids, who got autistic symptoms within a period of a few weeks of a vaccine. I think that the public health officials have been too quick to dismiss the hypothesis as irrational, without sufficient studies of causation. …*
>
> *The reason why they didn't want to look for those susceptibility groups was because they're afraid if they found them—however big or small they were—that that would scare the public away. First of all, I think the public's smarter than that; the public values vaccines. But, more importantly, I don't think you should ever turn your back on any scientific hypothesis because you're afraid of what it might show!*[55]

The CDC has also failed to address the science supporting a link between vaccines and autism.[56] For example, the CDC has not addressed a study which found a 300% increased rate of autism among newborns receiving the hepatitis B vaccine at birth compared to those that did not.[57] Nor a recent and first ever vaccinated vs. unvaccinated pilot study which found vaccinated

---

[51] Ibid.
[52] Studies of MMR and autism are also erroneous because of healthy user bias, which has been emphasized as a serious source of error in epidemiological vaccine safety studies by CDC scientists. https://doi.org/10.1093/oxfordjournals.aje.a116479
[53] http://www.cbsnews.com/news/the-open-question-on-vaccines-and-autism/
[54] Ibid.
[55] Ibid.
[56] https://www.cdc.gov/vaccinesafety/concerns/autism.html
[57] http://hisunim.org.il/images/documents/scientific_literature/Gallagher_Goodman_HepB_2010.pdf

children had a 420% increased rate of autism and that vaccinated preterm babies had an even higher rate of autism.[58] There is also a persuasive body of science supporting a clear connection between aluminum adjuvants in vaccines and autism which the CDC, despite numerous requests, has failed to directly or substantively address.[59] Letters from three aluminum adjuvant experts on this point are attached as Appendix C.

The critical need for HHS to properly engage in vaccine safety science regarding autism is made even more vital by the fact that vaccine makers are immune from liability for vaccine injury and vaccines are not safety-tested prior to licensure to assess whether they cause autism. Without proper long-term trials comparing those receiving the vaccine to an inert-placebo group, it is impossible to know prior to licensure whether these products cause autism. There are also no follow-up studies which compare vaccinated with unvaccinated individuals and hence no supportable basis to claim that vaccines do not cause any cases of autism. For the CDC to make this claim, it must demonstrate that a child receiving the entire vaccine schedule is at no greater risk of becoming autistic than a child that is unvaccinated. No such study has ever been done. The IOM Report referenced above has confirmed that the CDC cannot make this claim even for children receiving only the DTaP vaccine, let alone the entire vaccine schedule.

The 1986 Act expressly provides that you, as the Secretary, are to "develop and disseminate vaccine information materials for distribution by health care providers to the legal representatives of any child or to any other individual receiving a vaccine set forth in the Vaccine Injury Table." (42 U.S.C. § 300aa-26(a).) This section further provides that:

> The information in such materials shall be based on available data and information … and shall include … (1) a concise description of the benefits of the vaccine, (2) a concise description of the risks associated with the vaccine, (3) a statement of the availability of the National Vaccine Injury Compensation Program, and (4) such other relevant information as may be determined by the Secretary.

(42 U.S.C. § 300aa-26(c).) The VIS produced for every vaccine, including for DTaP, provides that other relevant information regarding the vaccine is available at the CDC website, www.cdc.gov.[60] The CDC website in turn claims that "Vaccines Do Not Cause Autism."[61] Since HHS has chosen to incorporate the CDC's website into the VIS as a resource, the information on that website regarding the relevant vaccine must be "based on available data and information." *Id*. But, based on available data and information, as highlighted by the IOM, HHS cannot validly claim that "Vaccines Do Not Cause Autism." Hence:

[58] http://www.oatext.com/pdf/JTS-3-186.pdf; http://www.oatext.com/pdf/JTS-3-187.pdf
[59] http://vaccine-safety.s3.amazonaws.com/WhitePaper-AlumAdjuvantAutism.pdf
[60] https://www.cdc.gov/vaccines/hcp/vis/current-vis.html
[61] https://www.cdc.gov/vaccinesafety/concerns/autism.html

(9) Please confirm that HHS shall forthwith remove the claim that "Vaccines Do Not Cause Autism" from the CDC website, or alternatively, please identify the specific studies on which HHS bases its blanket claim that no vaccines cause autism?

VII. Refusal to Conduct Vaccinated Versus Unvaccinated Study

The only scientifically valid way to answer a large portion of the questions raised regarding vaccine safety would be a long-term, properly powered and controlled study comparing the rate of all adverse events between vaccinated children and completely unvaccinated children. This is the same type of study required by HHS for every drug pre-licensure. HHS has nonetheless refused to conduct any such study, even retrospectively.

The need for this study is highlighted by the results of a few recent limited vaccinated vs. unvaccinated studies.

Dr. Peter Aaby is renowned for studying and promoting vaccines in Africa with over 300 published studies.[62] In 2017, he published a study finding children vaccinated with DTP were 10 times more likely to die in the first 6 months of life than the unvaccinated.[63] Dr. Aaby's study therefore concluded that: "All currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis."[64] More disturbing is that children vaccinated with DTP were dying from causes never associated with this vaccine, such as respiratory infections, diarrhea, and malaria.[65] This indicated that while DTP reduced the incidence of diphtheria, tetanus, and pertussis, it increased susceptibility to other infections.[66]

It is equally troubling that Dr. Abby's study was based on data that had been collecting dust for over 30 years[67] This begs the question: what other serious vaccine injuries are we missing because of neglect to conduct proper vaccine safety science.

A pilot study comparing 650 vaccinated and unvaccinated homeschooled children in the United States provides a glimpse of the potential scope of vaccine harm.[68] The study found that, compared to completely-unvaccinated children, fully-vaccinated children had an increased risk

---

[62] https://www.ncbi.nlm.nih.gov/pubmed/?term=PETER+AABY%5BAuthor+-+Full%5D

[63] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/ Dr. Aaby's study was more reliable than other vaccine safety studies because the subjects were accurately matched. An increasingly recognized problem in vaccine safety studies is that subjects are typically not well-matched. People with pre-existing health problems are reluctant to receive a vaccine, and are therefore unwittingly used as controls. When this happens, the control group is sicker than the vaccine-exposed group at the outset of the study. Studies with this problem give wrong results, and make the vaccine look much safer than it really is. Dr. Aaby's study was one of the few specifically designed to avoid this error.

[64] Ibid.

[65] Ibid.

[66] Ibid.

[67] Ibid.

[68] http://www.oatext.com/pdf/JTS-3-186.pdf

of 390% for allergies, 420% for ADHD, 420% for autism, 290% for eczema, 520% for learning disabilities, and 370% for any neuro-developmental delay.[69] Fully-vaccinated pre-term infants had an increased risk of 1,450% for a neurodevelopmental disorder, which includes a learning disability, ADHD or autism, compared to completely unvaccinated preterm infants.[70]

Another recent study compared children receiving the flu shot with those receiving a saline injection in a prospective randomized double-blind study.[71] Both groups had the same rate of influenza but the group receiving the flu shot had a 440% increased rate of non-influenza infection.[72] Like the DTP study, the flu vaccine increased susceptibility to other infections.

A properly sized vaccinated versus unvaccinated study is necessary and possible. As stated by the IOM in 2013: "It is possible to make this comparison through analyses of patient information contained in large databases such as VSD."[73] Senior CDC Scientist, Dr. Thompson similarly stated this type of study can and "needs to be done" but that the CDC is "not doing what they should be doing because they're afraid to look for things that might be associated."[74] When vaccine makers are generating over $33 billion in vaccine revenue annually and the CDC is spending over $5 billion annually to promote and purchase vaccines, there is no justification for not performing this study.[75]

The 1986 Act expressly provides that you, as the Secretary, "shall promote the development of childhood vaccines that result in fewer and less adverse reactions" and "shall make or assure improvements in … the … labeling, warning, … and research on vaccines, in order to reduce the risks of adverse reactions to vaccines." (42 U.S.C. § 300aa-27(a)(2).) Since comparing children receiving the vaccines recommended by the CDC with those that have not received any vaccines is the only scientifically valid way to assess the safety of the CDC's vaccine schedule:

(10) Please advise whether HHS intends to forthwith conduct adequately powered and controlled prospective as well as retrospective studies comparing total health outcomes of

---

[69] Ibid.

[70] http://www.oatext.com/pdf/JTS-3-187.pdf

[71] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/

[72] Ibid. *See also* http://vaccine-safety.s3.amazonaws.com/CDC_FOIA_Response_UnpublishedStudy.pdf (The CDC in 2001 apparently conducted a narrow vaccinated versus unvaccinated study comparing children receiving the Hepatitis B vaccine during the first month of life versus those who did not. The results of this study were never released by the CDC, and an abstract of the study was only recently obtained under a FOIA request. Children vaccinated with Hepatitis B vaccine in the first month of life, compared to children receiving no vaccines in the first month of life, had an increased risk of 829% for ADHD, 762% for autism, 638% for ADD, 565% for tics, 498% for sleep disorders, and 206% for speech delays. Note that while the abstract discusses comparing thimerosal exposure, since the only vaccine recommended by one month of age was Hepatitis B, and since only thimerosal containing Hepatitis B vaccine was available at the time of this study, this study appears to have primarily compared children receiving Hepatitis B with children that did not receive this vaccine.)

[73] https://www.nap.edu/read/13563/chapter/2#13

[74] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio

[75] https://www.hhs.gov/sites/default/files/fy2017-budget-in-brief.pdf; https://www.bccresearch.com/market-research/pharmaceuticals/vaccine-technologies-markets-report-phm014f.html

fully/partially vaccinated children with completely unvaccinated children?

VIII. Reducing Conflicts of Interest at HHS

The 1986 Act created a system in which vaccines are licensed, recommended, encouraged, subsidized, and defended by HHS. The 1986 Act's scheme thus places HHS in charge of two competing duties. On one hand, HHS is responsible for vaccine safety. On the other hand, HHS is required to promote vaccine uptake and defend against any claim they cause any harm.

Regrettably, it appears that HHS has chosen to focus almost entirely on its vaccine promotion and defense function to such a degree that it has essentially abandoned its vaccine safety function. To restore balance, HHS must take serious steps to create an "ethics firewall" between these competing functions. HHS also must take action with regard to its vaccine committee members and employees that have conflicts with vaccine makers.

HHS Licenses & Recommends Vaccines. With regard to the FDA's Vaccines and Related Biological Products Advisory Committee (**VRBPAC**), which effectively decides whether to license a vaccine, in 2000 the U.S. House Committee on Government Reform (the **Committee**) "determined that conflict of interest rules employed by the FDA and the CDC have been weak, enforcement has been lax, and committee members with substantial ties to pharmaceutical companies have been given waivers to participate in committee proceedings."[76] The Committee concluded of the VRBPAC: "The overwhelming majority of members, both voting members and consultants, have substantial ties to the pharmaceutical industry."[77]

With regard to the CDC's Advisory Committee on Immunization Practices (**ACIP**), which effectively decides whether to universally recommend a pediatric vaccine, the Committee found that ACIP members routinely fail to disclose conflicts with vaccine makers and when conflicts are disclosed "[t]he CDC grants blanket waivers to the ACIP members each year that allow them to deliberate on any subject, regardless of their conflicts."[78] The Committee drew focus on the vaccine most recently approved by the ACIP and found extensive and troubling conflicts of interest for most the ACIP members voting to recommend its universal use for children.[79] The Committee was further concerned that "ACIP liaison representatives have numerous ties to

---

[76] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf (For instance, "3 out of 5 FDA advisory committee [VRBPAC] members who voted to approve the rotavirus vaccine in December 1997 [then the most recently approved vaccine by the VRBPAC] had significant financial ties to pharmaceutical companies that were developing different versions of the vaccine.")

[77] Ibid.

[78] Ibid.

[79] Ibid. (The Committee's findings were that: (1) The chairman served on Merck's Immunization Advisory Board; (2) another member, who shared the patent on a rotavirus vaccine, had a $350,000 grant from Merck to develop the vaccine, and was a consultant for Merck; (3) another member was under contract with the Merck Vaccine Division, a principal investigator for SmithKline and received funds from various vaccine makers; (4) another member received a salary and other payments from Merck; (5) another member participated in vaccine studies with Merck, Wyeth, and SmithKline; and (6) another member received grants from Merck and SmithKline.)

vaccine manufacturers" but act like voting members of ACIP.[80] The Committee further took issue with the extensive conflicts of interests of members of ACIP's working groups which convene behind closed doors and whose recommendations are typically rubber stamped by the ACIP.[81] The Committee concluded that ACIP reflected "a system where government officials make crucial decisions affecting American children without the advice and consent of the governed."[82]

Despite the concerns the Committee expressed in its 2000 report, not much changed. A December 2009 report by the HHS Office of Inspector General found that the "CDC had a systemic lack of oversight of the ethics program for SGEs [a.k.a. **committee members**]".[83] For example, "Most of the experts who served on advisory panels in 2007 to evaluate vaccines for flu and cervical cancer had potential conflicts that were never resolved."[84]

In fact, the Inspector General found that the "CDC certified [conflict disclosure forms] with at least one omission in 2007 for 97 percent … of SGEs," "58 percent … of SGEs had at least one potential conflict of interest that CDC did not identify," and when the CDC identified a conflict, it improperly granted broad waivers despite being castigated for this improper practice in 2000.[85] Even worse, "32 percent … of SGEs … had at least one potential conflict of interest that CDC identified but did not resolve" and 13 percent of SGEs were allowed to participate in committee meetings without even having a conflict disclosure form on file.[86]

As the system is set up, an ACIP vote to recommend a vaccine, grants a vaccine manufacturer a liability-free market of 78 million American children, who are legally compelled to receive the vaccine, and billions of taxpayer dollars guaranteeing payment. In such a system, an ACIP vote must be completely insulated from any influence by the vaccine manufacturer. Instead, the opposite appears to be the norm.

HHS Promotes Vaccines. Moreover, while the CDC states on its website -- not less than 130 times -- that "CDC does not accept commercial support," this is simply not true.[87] For example, the British Medical Journal reported in 2015 that: "Despite the agency's disclaimer, the CDC does receive millions of dollars in industry gifts and funding, both directly and indirectly, and several recent CDC actions and recommendations have raised questions about the science it cites, the clinical guidelines it promotes, and the money it is taking."[88] As another example, pharmaceutical companies and other private entities, through the "CDC Foundation," can create and fund programs at the CDC (over half a billion dollars' worth to-date), endow positions at the

---

[80] Ibid.
[81] Ibid.
[82] Ibid.
[83] https://oig.hhs.gov/oei/reports/oei-04-07-00260.pdf
[84] http://www.nytimes.com/2009/12/18/health/policy/18cdc.html
[85] https://oig.hhs.gov/oei/reports/oei-04-07-00260.pdf (Splicing down this 58% of unidentified conflicts, 40% involved employment or grants, 13% involved equity ownership, and 5% involved consulting.)
[86] Ibid.
[87] https://search.cdc.gov/search?query=%22cdc+does+not+accept+commercial+support%22&utf8=%E2%9C%93&affiliate=cdc-main
[88] http://www.bmj.com/content/350/bmj.h2362

CDC, and even place individuals to work at the CDC, paid through "private funding." (42 U.S.C.A. § 280e-11(h)(1), (2).)

Worse, the promotion track for CDC management extends into vaccine makers. The most prominent example is former CDC Director Dr. Julie Gerberding, who headed the agency from 2002 through 2009. Dr. Gerberding oversaw several controversial studies regarding vaccines produced by Merck, which sought to silence those calling for an increase in the safety profile of those vaccines. When she left the CDC she was rewarded with the position of President of Merck Vaccines in 2010 with a reported $2.5 million annual salary and lucrative stock options.[89]

HHS Defends Vaccines. After HHS licenses, effectively mandates, and promotes a vaccine to 78 million American children with very limited safety data, this very same government agency is mandated to defend against any claim that the vaccine caused harm.

There is no other for-profit product where the very department responsible for regulating that product is statutorily required to promote its uptake and simultaneously defend against any claim it causes harm.

The Vaccine Injury Compensation Program (**VICP**) is effectively the only legal recourse in America to obtain compensation for a pediatric vaccine injury. (42 U.S.C. § 300aa-10 *et seq*.)[90] The injured must litigate against HHS and the DOJ in a quasi-judicial process filed under seal where the injured child effectively cannot obtain documents from or depose vaccine makers to prove how the vaccine caused injury. (§ 300aa-12.) DOJ and HHS have the government's vast resources, while the injured child must secure a private attorney. (§ 300aa-15.) Moreover, the injured child's damages are limited to $250,000 for death and pain and suffering. (*Id*.)

Worst of all, the injured child must almost always prove "causation" – the biological mechanism by which the vaccine injured the child.[91] Requiring an injured child to prove causation adds insult to injury because had HHS conducted the vaccine safety science it demands as proof in the VICP before licensing a vaccine, the child's injury may have been avoided altogether.

This truly is the epitome of injustice: requiring a child receiving a compulsory pharmaceutical product to medically prove to HHS how the vaccine caused his or her injury, where the science to understand vaccine injuries is not being done by the government department, HHS, tasked with this job.[92] As confirmed by the IOM, HHS has not conducted the basic science needed to even determine whether commonly claimed vaccine injuries are caused by vaccines.[93] It has failed to conduct even one properly sized study comparing vaccinated to

[89] https://www.sec.gov/cgi-bin/own-disp?action=getowner&CIK=0001628884
[90] *See also* Bruesewitz v. Wyeth LLC, 562 U.S. 223 (2011)
[91] http://www.gao.gov/assets/670/667136.pdf
[92] See Sections II, III, IV, V, VI, and VII above.
[93] See Section IV above.

unvaccinated children, despite all the resources at its disposal.[94] It is no wonder a single injured child's claim faces a high likelihood of failure in the VICP.

Many parents, doctors and scientists, as well as politicians, are legitimately concerned about the process whereby vaccines are licensed, recommended, promoted and defended by the same department. This is not because of any conspiracy, or belief an insidious intent. Rather, this system eliminates the incentive, and in fact creates a disincentive for HHS and vaccine makers, to conduct research to uncover long term chronic conditions, including the immune and neurological system disorders, which can result from the current vaccine schedule.

The 1986 Act expressly provides that you, as the Secretary, have at least equal and arguably greater responsibility for vaccine safety than for vaccine promotion. (42 U.S.C. §§ 300aa-2, 300aa-27.) In accordance with this statutory responsibility:

(11) Please advise if you will:

a. prohibit conflict waivers for members of HHS's vaccine committees (ACIP, VRBPAC, NVAC & ACCV)?
b. prohibit HHS vaccine committee members or HHS employees with duties involving vaccines from accepting any compensation from a vaccine maker for five years?
c. require that vaccine safety advocates comprise half of HHS's vaccine committees?
d. allocate toward vaccine safety an amount at least equal to 50% of HHS's budget for promoting/purchasing vaccines?
e. support the creation of a vaccine safety department independent of HHS?
f. support the repeal of the 1986 Act to the extent it grants immunity to pharmaceutical companies for injuries caused by their vaccine products?

IX. Conclusion

HHS can do better. With hundreds of vaccines in the pipeline it must do better. Children susceptible to vaccine injury are as deserving of protection as any other child. Avoiding injury to these children is not only a moral and ethical duty, but will in fact strengthen the vaccine program. Every parent that does not witness their child suffer a serious reaction after vaccination, such as a seizure or paralysis, is another parent that will not add their voice to the growing chorus of parents opposed to HHS's vaccine program due to safety concerns.

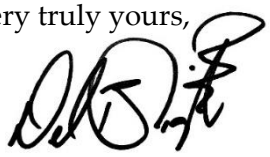
[94] See Section VII above.

Unless HHS performs its vital statutory obligations regarding vaccine safety, and until a frank conversation is possible regarding vaccine safety, children susceptible to vaccine injury will not be protected from such injuries. Nor will children injured by vaccines be able to access the services they need. We can do far better in protecting and serving children who are susceptible or succumb to serious injuries from vaccination. The first step in avoiding these harms and helping children already harmed is admitting there are deficiencies and working diligently to improve vaccine safety.

We respectfully request your attention to the important concerns outlined above and hope you agree that addressing these concerns is in everyone's best interest. These, in fact, reflect nothing more than what Congress already explicitly recognized when passing the 1986 Act: vaccines can and do cause serious injury and HHS needs to work diligently to identify and reduce these harms. If you would like to meet and discuss the foregoing, we would welcome that opportunity and hope to work cooperatively to address these issues.

If that is not possible, Congress, as a final resort to assure vaccine safety, authorized a "civil action … against the Secretary where there is alleged a failure of the Secretary to perform any act or duty under" the 1986 Act. (42 U.S.C. § 300aa-31(a).) We are prepared to authorize such an action and this letter constitutes the notice required by 42 U.S.C. § 300aa-31(b). It is, however, our hope that the vaccine safety issues identified herein can be resolved cooperatively, with all interested parties working together toward the common goal of vaccine safety entrusted to HHS under the 1986 Act.

Very truly yours,



Del Bigtree

cc: See Appendix A.
Enclosures: Appendices A to C.

Appendix A

A Voice For Choice
A Voice For Choice Advocacy
Christina Hildebrand, President
530 Showers Drive, Suite 7404
Mountain View, CA 94040

Alliance For Natural Health
Gretchen DuBeau, President
3525 Piedmont Road NE B6-310
Atlanta, GA 30305

Arizona Coalition Against Mandated Vaccines
Kelsey Davis, President
Gilbert, AZ 85212

Autism Action Network
John Gilmore, President
550 East Chester Street
Long Beach, NY 11561

Autism Giving Tree
Christina Stafford, M.Ed., BCBA, LBS, President
660 'W' Street
King of Prussia, PA 19406

AutismOne
Ed Arranga, President
1816 West Houston Avenue
Fullerton, CA 92833

The Canary Party
Jennifer Larson, President
6533 Flying Cloud Drive, Suite 1200
Eden Prairie, MN 55344

Colorado Coalition for Vaccine Choice
Fran Sincere, President
125 S. Zephyr
Lakewood, CO 80226

DAIR Foundation
Dawn Loughborough, President
10200 US HWY 290 West
Austin, TX 78736

Elizabeth Birt Center for Autism Law and Advocacy
Kim Mack Rosenberg, President
200 Cabrini Boulevard, Suite 66
New York, NY 10033

Enriched Parenting
Rebecca Fleischman, President
1208 Avenue M, Suite 2323
Brooklyn, NY 11230

Focus for Health Foundation
Shannon Mulvihill, R.N., Executive Director
776 Mountain Boulevard, Suite 202
Watchung, NJ 07069

Georgia Coalition for Vaccine Choice
Sandi Marcus, Founder/CEO
P.O. Box 45
Silver Creek, GA 30173

Health Choice
Mark Blaxil, President
6533 Flying Cloud Drive, Suite 1200
Eden Prairie, MN 55344

Health Choice Massachusetts
Candice Edwards, President
P.O. Box 175
Manchaug, MA 01526

Health Choice Maryland
Emily Tarsell, President
1501 Sulgrave Avenue, Suite 208
Baltimore, MD 21209

Health Choice Connecticut
Dr. Elissa Diamond Fields, President
P.O. Box 29
Roxbury, CT 06783

Health Freedom Florida
Dr. Ryan Fenn & MacKenzie Fraser, Co-Presidents
153 Ivernia Loop
Tallahassee, FL 32312

Health Freedom Idaho
Miste Gardner Karlfeldt, President
1045 S Ancona Ave Ste 140
Eagle, ID 83616

Healthcare Freedom Hawaii
Jessica McCormick &
Natasha Sky, Co-Directors
Mililani, HI 96789

Illinois Coalition for Informed Consent
Jen Suter &
Danielle Olson, Co-Directors
Jacksonville, IL 62650

Indiana for Medical Freedom
Melissa Sura, President
5424 Grapevine Drive
Indianapolis, IN 46235

Informed Choice Washington
Jena Dalpez, President
14106 93rd Avenue NE
Kirkland, WA 98034

Kentucky Vaccine Rights Coalition
Jennifer Benge & Ashley Kennedy, Co-Presidents
899 Corinth Road
Corbin, KY 40701

Know The Vax
Angela Gallagher, President
4553 Aldrich Avenue North
Minneapolis, MN 55412

Learn the Risk
Brandy Vaughan, President
3463 State Street, Suite 182
Santa Barbara, CA 93105

Louisiana Parents for Vaccine Rights
Melisha Dooley &
Sunny Dixon, Co-Directors
413 Toby Lane
Metairie, LA 70003

Maine Coalition for Vaccine Choice
Ginger Taylor, Director
11 High Street
Brunswick, ME 04011

March Against Monsanto
Tami Canal, President
7878 South 1960 East
South Weber, UT 84405

Michigan for Vaccine Choice
Suzanne M. Waltman, President
22615 Francis Street
St. Clair Shores, MI 48082

Minnesota Natural Health Coalition
Lee Beaty, President
1043 Grand Ave, Suite 317
St. Paul MN 55105

Minnesota Natural Health Legal Reform Project
Leo Cashman, President
1043 Grand Ave, Suite 317
St. Paul, MN 55105

Minnesota Vaccine Freedom Coalition
Angela Gallagher, President
4553 Aldrich Avenue North
Minneapolis, MN 55412

Mississippi Parents for Vaccine Rights
MaryJo Perry, President
P.O. Box 141
Pelahatchie, MS 39145

Missouri Parents Against Vaccines
Janessa Baake & Kendal Bourne, Co-Presidents
323 N. Fox Ridge Drive, Suite 204
Raymore, MO 64083

Moms Across America
Zen Honeycutt, President
24000 Alicia Parkway, Suite 17-236
Mission Viejo, CA 92691

Montanans For Medical Freedom
Edna Kent, Director
PO Box 1443
Florence, MT 59833

My Kids, My Choice
Rita Palma, President
2 Purdy Avenue
Baypoint, NY 11705

National Health Freedom Action
Jerri Johnson, President
PMB 218, 2136 Ford Parkway
St. Paul, MN 55116

National Health Freedom Coalition
Roseanne Lindsay, President
PMB 218, 2136 Ford Parkway
St. Paul, MN 55116

New York Alliance for Vaccine Rights
Aimee Villella McBride & Maria Gavriel, Co-Presidents
550 East Chester Street
Long Beach, NY 11561

Ohio Advocates for Medical Freedom
Robert M. Wise, President
P.O. Box 1236
Hartville, OH 44632

Oklahomans for Vaccine and Health Choice
Liza Greve, President
P.O. Box 721356
Norman, OK 73070

Organic Consumers Association
Ronnie Cummins, CEO
6771 South Silver Hill Dr.
Finland, MN 55603

Parents United 4 Kids
Stefanie Fetzer & Shawna Lambert, Co-Presidents
2925 Bonanza
San Clemente, CA 92673

People Advocating Vaccine Education, Inc.
Lisa Jillani, CEO
P.O. Box 690712
Charlotte, NC 28227

Physicians for Informed Consent
Dr. Shira Miller, Executive Director
13749 Riverside Drive
Sherman Oaks, CA 91423

Rogue Recovery
Tyler Dahm, President
3221 West 96th Avenue
Westminster, CO 80031

South Carolina Health Coalition
Jennifer Black & Rebekah Watson, Co-Presidents
1754 Woodruff Road, Suite 112
Greenville, SC 29607

Spectrum Revolution
Catharine Layton, President
357 S. Earlham Street
Orange, CA 92869

Tennessee Coalition for Vaccine Choice
Kristen Odom-Holland, President
P.O. Box 4508
Chattanooga, TN 37405

Vaccine Injury Awareness League
Michelle Ford, President
10866 Washington Blvd, Suite 65
Culver City, CA 90232

Vaccine Safety Council Minnesota
Patti Carroll, President
6533 Flying Cloud Drive, Suite 1200
Eden Prairie, MN 55344

Vermont Coalition for Vaccine Choice
Jennifer Stella, President
P.O. Box 74
Waitsfield, VT 05673

Virginians for Health Freedom
Deborah Hommer, President
P.O. Box 2015
Spotsylvania, VA 22553

West Virginians for Health Freedom
Dr. Chanda Adkins, Director
108 Yorktown Court
Beckley, WV 25801

Weston A. Price Foundation
Sally Fallon Morell, President
PMB 106-380, 4200 Wisconsin Avenue NW
Washington, D.C., 20016

World Mercury Project
Robert F. Kennedy, Jr., Chairman
1227 North Peachtree Parkway, Suite 202
Peachtree City, GA 3026

Appendix B

Adverse Effects of Vaccines

Evidence and Causality

Committee to Review Adverse Effects of Vaccines

Board on Population Health and Public Health Practice

Kathleen Stratton, Andrew Ford, Erin Rusch, and Ellen Wright Clayton,
Editors

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and ataxia.

Mechanistic Evidence

The committee identified one publication reporting the development of ataxia after the administration of DTaP vaccine. Kubota and Takahashi (2008) did not provide evidence of causality beyond a temporal relationship of 2 days between vaccine administration and development of cerebellar symptoms leading to a diagnosis of acute cerebellar ataxia. The publication did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and ataxia as lacking.

Causality Conclusion

Conclusion 10.5: The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and ataxia.

AUTISM

Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of autism after the administration of DTaP vaccine. This one study (Geier and Geier, 2004) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism.

Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of autism after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

Weight of Mechanistic Evidence

The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism as lacking.

Causality Conclusion

Conclusion 10.6: The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccines and ADEM.

Mechanistic Evidence

The committee identified five publications of ADEM developing after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens alone or in combination. Four publications did not provide evidence beyond temporality, one of which was deemed too short based on the possible mechanisms involved (Abdul-Ghaffar and Achar, 1994; Bolukbasi and Ozmenoglu, 1999; Hamidon and Raymond, 2003; Rogalewski et al., 2007). In addition, Rogalewski et al. (2007) reported the administration of vaccines against hepatitis B, hepatitis A, and poliovirus in

Appendix C

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

Faculty of Medicine
Department of Ophthalmology
& Visual Sciences
Shaw Laboratory
828 West 10th Avenue, Room 386
Vancouver, BC Canada V5Z 1L8

Phone 604 875 4111 Local 68375
Fax 604 875 4376
www.neuraldynamicsubc.ca

June 24, 2017

United States Department of Health & Human Services
National Institutes of Health
Food & Drug Administration
Centers for Disease Control & Prevention
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *Aluminum Adjuvants*

Dear Directors:

I am writing to you in regard to aluminum adjuvants in vaccines. This subject is one my laboratory works on intensively and therefore one where I feel that I have some expertise. In particular, we have studied the impact of aluminum adjuvants in animal models of neurological disease, including autism spectrum disorder (ASD). Our relevant studies on the general topic of aluminum neurotoxicity in general and specifically in regard to adjuvants are cited below.

These studies and the broader existing literature regarding aluminum toxicity, lead almost invariably to the conclusion that aluminum in any chemical form is always neurotoxic when administered to humans. Further, I am convinced that aluminum adjuvants in vaccines may contribute to neurological disorders across the lifespan. In adults, such adjuvant may induce macrophagic myofasciitis, a disease with neuropathological aspects. In children, there is growing evidence that aluminum adjuvants may disrupt developmental processes in the central nervous system and therefore contribute to ASD in susceptible children.

Despite the foregoing, the safety of aluminum adjuvants in vaccines has not been properly studied in humans even though, pursuant to the recommended vaccine schedule published by the Centers for Disease Control (CDC), a baby may be injected with up to 3,675 micrograms of aluminum adjuvant by six months of age.

In regard to the above, it is my belief that the CDC's claim on its website that "Vaccines Do Not Cause Autism" is wholly unsupported. Given this, I remain convinced that much more research on the role of aluminum adjuvant in vaccines and neurological disorders, including ASD, is warranted and should be a research priority for the NIH and other funding bodies.

Yours sincerely,

Christopher A. Shaw, Ph.D
Professor
Dept. of Ophthalmology and Visual Sciences
University of British Columbia
828 W. 10th Ave.
Vancouver, British Columbia
Canada, V5Z1M9
Tel: 604-875-4111 (ext. 68373)
Email: cashawlab@gmail.com

Relevant Publications (Shaw Laboratory)

1. Crepeaux G, Eidi H, David MO, Baba-Amer Y, Tzavara E, giros B, authier FJ, Exley C, Shaw CA, Cadusseau J, Gherardi RK. Non-linear dose-response of aluminium hydroxide adjuvant particles: Selective dose neurotoxicity. *Toxicology*. 375:48-57. (2016).

2. Crepeaux G, Eidi H, David M-O, Tzavara E, Giros B, Exley C, Curmi PA, Shaw CA, Gherardi RK, Cadusseau J. Highly delayed systemic translocation of aluminium-based adjuvant in CD1 mice following intramuscular injections. *J. Inorg. Biochem*. 152:199-205. (2015).

3. Shaw CA, Li D, Tomljenovic L. Are there negative CNS impacts of aluminum adjuvants in vaccines and immunotherapy? *Immunotherapy*. 6 (10):1055-1071. (2014).

4. Shaw CA, Seneff S, Kette SD, Tomljenovic L, Oller Jr JW, Davidson RM. Aluminum–induced entropy in biological systems: Implications for neurological disease. *J Toxicology*. Volume 2014, Article ID 491316. (2014).

5. Shaw CA, Kette SD, Davidson RM, Seneff S. Aluminum's role in CNS-immune system interactions leading to neurological disorders. *Immunome Res*. 9:1.

6. Shaw CA, Marler TE. Aluminum and the human diet revisited. In: Communicative & Integrative Biology; *Landes Bioscience*. 6:e26369. (2013).

7. Shaw CA, Tomljenovic L. Aluminum in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity. *Immunol Res*. (2013).

8. Shaw CA, Li Y, Tomljenovic L. Administration of aluminum to neonatal mice in vaccine in vaccine-relevant amounts is associated with adverse long term neurological outcomes. *J Inorg Chem*. (2013).

9. Tomljenovic L, Shaw CA. Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations. *Lupus*. 21:223-230. (2012).

10. Tomljenovic L and Shaw CA. Editorial, Special Issue: The Biochemistry/Toxicity of Aluminum. *Current Inorganic Chemistry*. 2(1): 1-2. (2012).

11. Tomljenovic L and Shaw CA. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? *J Inorg Biochem*. 105(11):1489-99. (2011).

12. Tomljenovic L and Shaw CA. Aluminum vaccine adjuvants: Are they safe? *Current Medicinal Chemistry*. 18:2630 – 2637. (2011).

13. Shaw CA and Petrik MS. Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration. *J Inorganic Biochem*. 103 (11): 1555-62. (2009).

14. Petrik MS, Wong MC, Tabata RC, Garry RF, and Shaw CA. Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice. *J Neuromolecular Medicine*. 9: 83-100. (2007).

institutmondor
de recherche biomédicale

UNIVERSITÉ
PARIS-EST

June 15, 2017

United States Department of Health & Human Services
National Institutes of Health
Food & Drug Administration
Centers for Disease Control & Prevention
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *Aluminum Adjuvants*

Dear Directors:

I am an expert in the field of aluminum adjuvants toxicity in humans and animal models. I have been working in this field since the initial description of the AI vaccine-induced macrophagic myofasciitis in 1998. Since that time I have written 40 peer-reviewed scientific publications and one book on this subject.

I strongly support the contention that aluminum adjuvants in vaccines may have a role in the etiology of autism spectrum disorder (ASD). My view is founded on a significant and burgeoning body of peer-reviewed scientific evidence which makes the link between ASD and exposure to aluminum through vaccinations and other sources. Examples of this literature from my own group are detailed below and I urge the HHS to take them into consideration in forming any future opinion on the safety of aluminum adjuvants in vaccines.

The Center for Disease Control's claim on its website that "Vaccines Do Not Cause Autism" is unsupported with respect to aluminum adjuvants and this claim stifles the important research to determine the safety of aluminum adjuvants used in vaccines. As an expert in the field of aluminum adjuvants and aluminum toxicity I solemnly declare that more research on the role of aluminum adjuvant in vaccines and neurological disorders, including ASD, is essential and urgently required.

Yours very sincerely

Romain K. Gherardi
Professor, Neuromuscular Pathology Expert Centre
University Paris-Est, INSERM U955-E10,
Henri Mondor hospital, Créteil France
Contact at the hospital
Tel 00 (33) 1 49812746
romain.gherardi@hmn.aphp.fr

UMR U955 INSERM / UPEC

Team 10
« Biology of the neuromuscular system»

Fred Relaix, director
FrançoisJérome Authier, co-director

Romain Gherardi, former director
Tél. +33 (0)1 49 81 27 42
Fax. +33 (0)1 49 81 27 33
romain .gherardi@inserm.fr

Selection of significant publications from our group in the field

Gherardi R. Toxic Story: deux ou trois vérités embarrassantes sur les adjuvants des vaccins. **Actes Sud** (publisher), Paris, 2016, 250 pages

Crépeaux G, Eidi H, David MO, Baba-Amer Y, Tzavara E, Giros B, Authier FJ, Exley C, Shaw CA, Cadusseau J, Gherardi RK. Non-linear dose-response of aluminium hydroxide adjuvant particles: Selective low dose neurotoxicity. **Toxicology**. 2017 Jan 15;375:48-57.

Masson JD, Crépeaux G, Authier FJ, Exley C, Gherardi RK. [Critical analysis of reference studies on aluminium-based adjuvants toxicokinetics]. **Ann Pharm Fr**. 2017 May 30. pii: S0003-4509(17)30033-0.

Van Der Gucht A, Aoun Sebaiti M, Guedj E, Aouizerate J, Yara S, Gherardi RK, Evangelista E, Chalaye J, Cottereau AS, Verger A, Bachoud-Levi AC, Abulizi M, Itti E, Authier FJ. Brain (18)F-FDG PET Metabolic Abnormalities in Patients with Long-Lasting Macrophagic Myofascitis**. J Nucl Med**. 2017 Mar;58(3):492-498.

Crépeaux G, Eidi H, David MO, Tzavara E, Giros B, Exley C, Curmi PA, Shaw CA, Gherardi RK, Cadusseau J. Highly delayed systemic translocation of aluminum-based adjuvant in CD1 mice following intramuscular injections. **J Inorg Biochem**. 2015 Nov;152:199-205.

Eidi H, David MO, Crépeaux G, Henry L, Joshi V, Berger MH, Sennour M, Cadusseau J, Gherardi RK, Curmi PA. Fluorescent nanodiamonds as a relevant tag for the assessment of alum adjuvant particle biodisposition. **BMC Med.** 2015 Jun 17;13:144.

Van Der Gucht A, Aoun Sebaiti M, Itti E, Aouizerate J, Evangelista E, Chalaye J, Gherardi RK, Ragunathan-Thangarajah N, Bachoud-Levi AC, Authier FJ. Neuropsychological Correlates of Brain Perfusion SPECT in Patients with Macrophagic Myofasciitis. **PLoS One**. 2015 Jun 1;10(6):e0128353.

Khan Z, Combadière C, Authier FJ, Itier V, Lux F, Exley C, Mahrouf-Yorgov M, Decrouy X, Moretto P, Tillement O, Gherardi RK, Cadusseau J. Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. **BMC Med.** 2013 Apr 4;11:99.

Couette M, Boisse MF, Maison P, Brugieres P, Cesaro P, Chevalier X, Gherardi RK, Bachoud-Levi AC, Authier FJ. Long-term persistence of vaccine-derived aluminum hydroxide is associated with chronic cognitive dysfunction**. J Inorg Biochem**. 2009 Nov;103(11):1571-8.

Authier FJ, Sauvat S, Christov C, Chariot P, Raisbeck G, Poron MF, Yiou F, Gherardi R. AlOH3-adjuvanted vaccine-induced macrophagic myofasciitis in rats is influenced by the genetic background. **Neuromuscul Disord**. 2006 May;16(5):347-52.

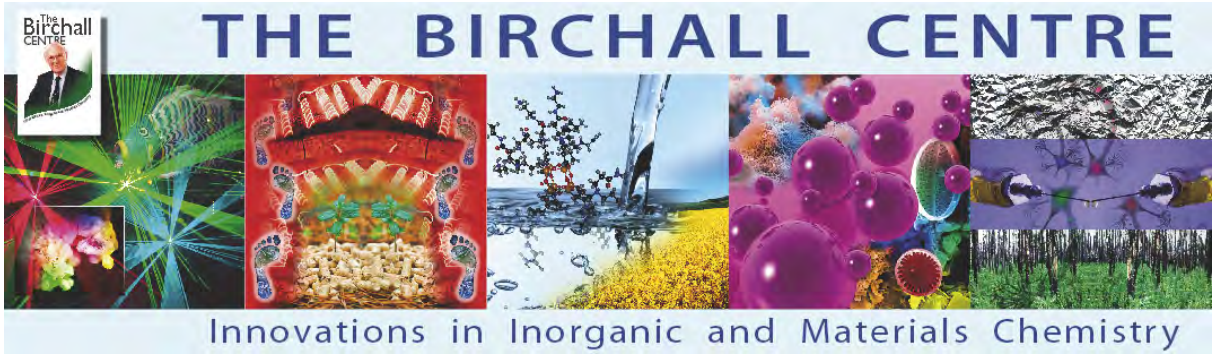
Authier FJ, Sauvat S, Champey J, Drogou I, Coquet M, Gherardi RK. Chronic fatigue syndrome in patients with macrophagic myofasciitis. **Arthritis Rheum. 2003** Feb;48(2):569-70.

Gherardi RK. [Lessons from macrophagic myofasciitis: towards definition of a vaccine adjuvant-related syndrome]. **Rev Neurol** (Paris). 2003 Feb;159(2):162-4. Review. French.

Authier FJ, Cherin P, Creange A, Bonnotte B, Ferrer X, Abdelmoumni A, Ranoux D, Pelletier J, Figarella-Branger D, Granel B, Maisonobe T, Coquet M, Degos JD, Gherardi RK. Central nervous system disease in patients with macrophagic myofasciitis. **Brain. 2001** May;124(Pt 5):974-83.

Gherardi RK, Coquet M, Cherin P, Belec L, Moretto P, Dreyfus PA, Pellissier JF, Chariot P, Authier FJ. Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. **Brain. 2001** Sep;124(Pt 9):1821-31.

Gherardi RK, Coquet M, Chérin P, Authier FJ, Laforêt P, Bélec L, Figarella-Branger D, Mussini JM, Pellissier JF, Fardeau M. Macrophagic myofasciitis: an emerging entit. **Lancet. 1998** Aug 1;352(9125):347-52.



Tel: 01782 734080
Fax: 01782 712378
e-mail: c.exley@keele.ac.uk
http://www.keele.ac.uk/aluminium

June 15, 2017

United States Department of Health & Human Services
National Institutes of Health
Food & Drug Administration
Centers for Disease Control & Prevention
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *Aluminum Adjuvants*

Dear Directors:

I am an expert in the field of aluminum adjuvants and aluminum toxicity. I have been working in this field for more than 30 years during which time I have written in excess of 150 peer-reviewed scientific publications on this subject.

I strongly support the contention that aluminum adjuvants in vaccines may have a role in the etiology of autism spectrum disorder (ASD). My view is founded on a significant and burgeoning body of peer-reviewed scientific evidence which makes the link between ASD and exposure to aluminum through vaccinations and other sources. Examples of this literature from my own group are detailed below and I urge the HHS to take them into consideration in forming any future opinion on the safety of aluminum adjuvants in vaccines.

The Center for Disease Control's claim on its website that "Vaccines Do Not Cause Autism" is unsupported with respect to aluminum adjuvants and this claim stifles the important research to determine the safety of aluminum adjuvants used in vaccines. As an expert in the field of aluminum adjuvants and aluminum toxicity I solemnly declare that more research on the role of aluminum adjuvant in vaccines and neurological disorders, including ASD, is essential and urgently required.

Yours faithfully

Christopher Exley PhD
Professor in Bioinorganic Chemistry

Honorary Professor, University of the Highlands and Islands

List of Recent, Relevant and Significant Publications From Our Group

Exley C, Siesjö P & Eriksson H (2010) The immunobiology of aluminium adjuvants: how do they really work? Trends in Immunology 31, 103-109.

Exley C and House E (2011) Aluminium in the human brain. Monatshefte für Chemie - Chemical Monthly 142, 357-363.

House E, Esiri M, Forster G, Ince PG and Exley C (2012) Aluminium, iron and copper in human brain tissues donated to the medical research council's cognitive function and ageing study. Metallomics 4, 56-65.

Exley C (2011) Aluminium-based adjuvants should not be used as placebos in clinical trials. Vaccine 29, 9289.

Exley C (2012) When an aluminium adjuvant is not an aluminium adjuvant used in human vaccination programmes. Vaccine 30, 2042.

Exley C (2012) The coordination chemistry of aluminium in neurodegenerative disease. Coordination Chemistry Reviews 256, 2142-2146.

Exley C, House E, Polwart A and Esiri MM (2012) Brain burdens of aluminium, iron and copper and their relationships with amyloid beta pathology in 60 human brains. Journal of Alzheimer's Disease 31, 725-730.

Davenward S, Bentham P, Wright J, Crome P, Job, D, Polwart A and Exley C (2013) Silicon-rich mineral water as a non-invasive test of the 'aluminium hypothesis' in Alzheimer's disease. Journal of Alzheimer's Disease 33, 423-430.

Khan Z, Combadière C, Authier FJ, Itier V, Lux F, Exley C, Mahrouf-Yorgov M, Decrouy X, Moretto P, Tillement O, Gherardi RK, and Cadusseau J (2013) Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. BMC Medicine 11:99.

Exley C (2013) Human exposure to aluminium. Environmental Science:Processes and Impacts 15, 1807-1816.

Ohlsson L, Exley C, Darabi A, Sandén E, Siesjö P and Eriksson H (2013) Aluminium based adjuvants and their effects on mitochondria and lysosomes of phagocytosing cells. Journal of Inorganic Biochemistry 128, 229-236.

Exley C (2014) Aluminium adjuvants and adverse events in sub-cutaneous allergy immunotherapy. Allergy, Asthma and Clinical Immunology 10, 4.

Exley C and Vickers T (2014) Elevated brain aluminium and early onset Alzheimer's disease in an individual occupationally exposed to aluminium: a case report. Journal of Medical Case Reports 8,41.

Exley C (2014) What is the risk of aluminium as a neurotoxin? Expert Review of Neurotherapeutics 14, 589-591.

Mold M, Eriksson H, Siesjö P, Darabi A, Shardlow E and Exley C (2014) Unequivocal identification of intracellular aluminium adjuvant in a monocytic THP-1 cell line. Scientific Reports 4, 6287.

Exley C (2014) Why industry propaganda and political interference cannot disguise the inevitable role played by human exposure to aluminium in neurodegenerative diseases, including Alzheimer's disease. Frontiers in Neurology **5**:212. doi: 10.3389/fneur.2014.00212.

Crépeaux G, Eidi H, David M-O, Tzavara E, Giros B, Exley C, Curmi PA, Shaw CA, Gherardi RK and Cadusseau J (2015) Highly delayed systemic translocation of aluminium-based adjuvant in CD1 mice following intramuscular injections. Journal of Inorganic Biochemistry 152, 199-205.

Exley C (2016) The toxicity of aluminium in humans. Morphologie 100, 51-55.

Mirza A, King A, Troakes C and Exley C (2016) The identification of aluminium in human brain tissue using lumogallion and fluorescence microscopy. Journal of Alzheimer's Disease 54, 1333-1338.

Mold M, Shardlow E and Exley C (2016) Insight into the cellular fate and toxicity of aluminium adjuvants used in clinically-approved human vaccinations. Scientific Reports 6:31578.

Mirza A, King A, Troakes C and Exley C (2017) Aluminium in brain tissue in familial Alzheimer's disease. Journal of Trace Elements in Medicine and Biology 40, 30-36.

Shardlow E, Mold M and Exley C (2017) From stock bottle to vaccine: Elucidating the particle size distributions of aluminium adjuvants using dynamic light scattering. Frontiers in Chemistry 4, 48.

Exley C (2017) Aluminium should now be considered a primary aetiological factor in Alzheimer's disease. Journal of Alzheimer's Disease Reports 1, 23-25.

Telephone number +44 (01782) 584211
Fax +44 (01782) 712378

Keele University, Staffordshire, ST5 5BG United Kingdom
Telephone number +44 (01782) 621111 http://www.keele.ac.uk

Footnote 14

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RECOMBIVAX HB safely and effectively. See full prescribing information for RECOMBIVAX HB.

RECOMBIVAX HB® Hepatitis B Vaccine (Recombinant)
Suspension for intramuscular injection
Initial U.S. Approval: 1986

----------RECENT MAJOR CHANGES ----------
Dosage and Administration (2) 12/2018

----------INDICATIONS AND USAGE ----------
RECOMBIVAX HB is a vaccine indicated for prevention of infection caused by all known subtypes of hepatitis B virus. RECOMBIVAX HB is approved for use in individuals of all ages. RECOMBIVAX HB Dialysis Formulation is approved for use in predialysis and dialysis patients 18 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
RECOMBIVAX HB
- Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule. (2.1)
- Adolescents 11 through 15 years of age: A series of either 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule or a series of 2 doses (1.0 mL) on a 0- and 4- to 6-month schedule). (2.1)
- Persons 20 years of age and older: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule. (2.1)

RECOMBIVAX HB Dialysis Formulation
- Adults on predialysis or dialysis: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
RECOMBIVAX HB is a sterile suspension available in the following presentations:
- 0.5 mL (5 mcg) Pediatric/Adolescent Formulation single-dose vials and prefilled syringes (3, 11, 16.1)
- 1 mL (10 mcg) Adult Formulation single-dose vials and prefilled syringes (3, 11, 16.1)

RECOMBIVAX HB Dialysis Formulation is a sterile suspension available in the following presentation:
- 1 mL (40 mcg) single-dose vials (3, 11, 16.1)

----------CONTRAINDICATIONS ----------
Severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of RECOMBIVAX HB, including yeast. (4, 11)

---------- WARNINGS AND PRECAUTIONS ----------

The vial stopper, the syringe plunger stopper, and tip cap contain dry natural latex rubber which may cause allergic reactions in latex-sensitive individuals. (5.1)

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including RECOMBIVAX HB, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.2)

---------- ADVERSE REACTIONS ----------
In healthy infants and children (up to 10 years of age), the most frequently reported systemic adverse reactions (>1% injections), in decreasing order of frequency, were irritability, fever, diarrhea, fatigue/weakness, diminished appetite, and rhinitis. (6.1)
In healthy adults, injection site reactions and systemic adverse reactions were reported following 17% and 15% of the injections, respectively. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS ----------
Do not mix RECOMBIVAX HB with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RECOMBIVAX HB® [Hepatitis B Vaccine, Recombinant] is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. RECOMBIVAX HB is approved for use in individuals of all

ages. RECOMBIVAX HB Dialysis Formulation is approved for use in adult predialysis and dialysis patients 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration. See Section 2.2 for subcutaneous administration in persons with hemophilia.

RECOMBIVAX HB should be administered as soon as possible after being removed from refrigeration *[see How Supplied/Storage and Handling (16)]*.

2.1 Dosage and Schedule

RECOMBIVAX HB:

Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule.

Adolescents 11 through 15 years of age: A series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule or a series of 2 doses (1.0 mL each) on a 0- and 4- to 6-month schedule.

Persons 20 years of age and older: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule.

RECOMBIVAX HB Dialysis Formulation:

Adults on predialysis and dialysis: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule.

Table 1 summarizes the dose and formulation of RECOMBIVAX HB for specific populations, regardless of the risk of infection with hepatitis B virus.

Table 1: RECOMBIVAX HB Recommended Dose and Administration Schedules

Group	Dose/Regimen
Infants*, Children and Adolescents 0-19 years of age (Pediatric/Adolescent Formulation)	5 mcg (0.5 mL) 3 doses at 0, 1, and 6 months
Adolescents† 11 through 15 years of age (Adult formulation)	10 mcg‡ (1.0 mL) 2 doses at 0 and 4-6 months
Adults ≥20 years of age (Adult formulation)	10 mcg‡ (1.0 mL) 3 doses at 0, 1, and 6 months
Predialysis and Dialysis Patients§ (Dialysis formulation)	40 mcg (1.0 mL) 3 doses at 0, 1, and 6 months

* For specific recommendations for infants see ACIP recommendations.{1}

† Adolescents (11 through 15 years of age) may receive either regimen: 3 x 5 mcg (Pediatric Formulation) or 2 x 10 mcg (Adult Formulation).

‡ If the suggested dose (10 mcg) is not available, the appropriate dosage can be achieved with two 5 mcg doses. However, the Dialysis Formulation may be used only for adult predialysis/dialysis patients.

§ See also recommendations for revaccination of predialysis and dialysis patients in *[Dosage and Administration (2.4)]*.

2.2 Preparation and Administration

Shake the single-dose vial or single-dose prefilled syringe well to obtain a slightly opaque, white suspension before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if the suspension does not appear homogeneous or if extraneous particulate matter remains or if discoloration is observed.

For single-dose vials, withdraw and administer entire dose of RECOMBIVAX HB intramuscularly using a sterile needle and syringe.

For single-dose prefilled syringes, securely attach a needle by twisting in a clockwise direction and administer dose of RECOMBIVAX HB intramuscularly.

The deltoid muscle is the preferred site for intramuscular injection for adults, adolescents and children 1 year of age and older whose deltoid is large enough for intramuscular injection. The anterolateral aspect of the thigh is the preferred site for intramuscular injection for infants younger than 1 year of age. RECOMBIVAX HB should not be administered in the gluteal region, as injections given in the buttocks have resulted in lower seroconversion rates than expected.{2}

RECOMBIVAX HB may be administered subcutaneously to persons at risk for hemorrhage following intramuscular injections (e.g., hemophiliacs). However, hepatitis B vaccines are known to result in lower antibody response when administered subcutaneously.{3} Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, consider subcutaneous administration only in persons who are at risk of hemorrhage following intramuscular injections.

Do not administer intravenously or intradermally.

2.3 Known or Presumed Exposure to Hepatitis B Virus

Known or Presumed Exposure to HBsAg

Refer to recommendations of the Advisory Committee on Immunization Practices (ACIP) and to the package insert for hepatitis B immune globulin (HBIG) for management of persons with known or presumed exposure to the hepatitis B virus (e.g., neonates born of infected mothers or persons who experienced percutaneous or permucosal exposure to the virus). When recommended, administer RECOMBIVAX HB and HBIG intramuscularly at separate sites (e.g., opposite anterolateral thighs for exposed neonates) as soon as possible after exposure. Administer additional doses of RECOMBIVAX HB (to complete a vaccination series) in accordance with ACIP recommendations.

2.4 Booster Vaccinations

The duration of the protective effect of RECOMBIVAX HB in healthy vaccinees is unknown at present and the need for booster doses is not yet defined. The ACIP provides recommendations for use of a booster dose or revaccination series in previously vaccinated individuals with known or presumed exposure to Hepatitis B Virus.

Consider a booster dose or revaccination with RECOMBIVAX HB Dialysis Formulation (blue color code) in predialysis/dialysis patients if the anti-HBs level is less than 10 mIU/mL at 1 to 2 months after the third dose. Assess the need for a booster dose annually by antibody testing, and give a booster dose when the anti-HBs level declines to less than 10 mIU/mL.{3}

3 DOSAGE FORMS AND STRENGTHS

RECOMBIVAX HB is a sterile suspension available in the following presentations:

- 0.5 mL (5 mcg) Pediatric/Adolescent Formulation single-dose vials and prefilled syringes
- 1 mL (10 mcg) Adult Formulation single-dose vials and prefilled syringes

RECOMBIVAX HB DIALYSIS FORMULATION is a sterile suspension available in the following presentation:

- 1 mL (40 mcg) single-dose vial *[see Description (11) and How Supplied/Storage and Handling (16)]*

4 CONTRAINDICATIONS

Do not administer RECOMBIVAX HB to individuals with a history of severe allergic or hypersensitivity reactions (*e.g.*, anaphylaxis) after a previous dose of any hepatitis B-containing vaccine or to any component of RECOMBIVAX HB, including yeast *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity to Latex

The vial stopper and the syringe plunger stopper and tip cap contain dry natural latex rubber, which may cause allergic reactions in latex-sensitive individuals.

5.2 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including RECOMBIVAX HB, to infants born prematurely should be based on consideration of the individual infant's medical status and the

potential benefits and possible risks of vaccination. For RECOMBIVAX HB, this assessment should include consideration of the mother's hepatitis B antigen status and the high probability of maternal transmission of hepatitis B virus to infants born to mothers who are HBsAg positive if vaccination is delayed.

5.3 Infants Weighing Less Than 2000 g

Hepatitis B vaccination should be delayed until 1 month of age or hospital discharge in infants weighing <2000 g if the mother is documented to be HBsAg negative at the time of the infant's birth. Infants weighing <2000 g born to HBsAg positive or HBsAg unknown mothers should receive vaccine and hepatitis B immune globulin (HBIG) in accordance with ACIP recommendations if HBsAg status cannot be determined{3} *[see Dosage and Administration (2)].*

5.4 Prevention and Management of Allergic Vaccine Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration *[see Contraindications (4)].*

5.5 Limitations of Vaccine Effectiveness

Hepatitis B virus has a long incubation period. RECOMBIVAX HB may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccination. Additionally, vaccination with RECOMBIVAX HB may not protect all individuals.

6 ADVERSE REACTIONS

In healthy infants and children (up to 10 years of age), the most frequently reported systemic adverse reactions (>1% injections), in decreasing order of frequency, were irritability, fever, diarrhea, fatigue/weakness, diminished appetite, and rhinitis. In healthy adults, injection site reactions and systemic adverse reactions were reported following 17% and 15% of the injections, respectively.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In three clinical studies, 434 doses of RECOMBIVAX HB, 5 mcg, were administered to 147 healthy infants and children (up to 10 years of age) who were monitored for 5 days after each dose. Injection site reactions and systemic adverse reactions were reported following 0.2% and 10.4% of the injections, respectively. The most frequently reported systemic adverse reactions (>1% injections), in decreasing order of frequency, were irritability, fever (≥101°F oral equivalent), diarrhea, fatigue/weakness, diminished appetite, and rhinitis.

In a study that compared the three-dose regimen (5 mcg) with the two-dose regimen (10 mcg) of RECOMBIVAX HB in adolescents, the overall frequency of adverse reactions was generally similar.

In a group of studies, 3258 doses of RECOMBIVAX HB, 10 mcg, were administered to 1252 healthy adults who were monitored for 5 days after each dose. Injection site reactions and systemic adverse reactions were reported following 17% and 15% of the injections, respectively. The following adverse reactions were reported:

Incidence Equal To or Greater Than 1% of Injections

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Injection site reactions consisting principally of soreness, and including pain, tenderness, pruritus, erythema, ecchymosis, swelling, warmth, nodule formation.

The most frequent systemic complaints include fatigue/weakness; headache; fever (≥100°F); malaise.

GASTROINTESTINAL DISORDERS

Nausea; diarrhea

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Pharyngitis; upper respiratory infection

Incidence Less Than 1% of Injections

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Sweating; achiness; sensation of warmth; lightheadedness; chills; flushing

GASTROINTESTINAL DISORDERS

Vomiting; abdominal pains/cramps; dyspepsia; diminished appetite

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Rhinitis; influenza; cough

NERVOUS SYSTEM DISORDERS
Vertigo/dizziness; paresthesia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Pruritus; rash (non-specified); angioedema; urticaria
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Arthralgia including monoarticular; myalgia; back pain; neck pain; shoulder pain; neck stiffness
BLOOD AND LYMPHATIC DISORDERS
Lymphadenopathy
PSYCHIATRIC DISORDERS
Insomnia/disturbed sleep
EAR AND LABYRINTH DISORDERS
Earache
RENAL AND URINARY DISORDERS
Dysuria
CARDIAC DISORDERS
Hypotension

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported with use of the marketed vaccine. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to a vaccine exposure.

Immune System Disorders

Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria have been reported within the first few hours after vaccination. An apparent hypersensitivity syndrome (serum-sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as urticaria, erythema multiforme, ecchymoses and erythema nodosum *[see Warnings and Precautions (5.1)]*. Autoimmune diseases including systemic lupus erythematosus (SLE), lupus-like syndrome, vasculitis, and polyarteritis nodosa have also been reported.

Gastrointestinal Disorders

Elevation of liver enzymes; constipation

Nervous System Disorders

Guillain-Barré syndrome; multiple sclerosis; exacerbation of multiple sclerosis; myelitis including transverse myelitis; seizure; febrile seizure; peripheral neuropathy including Bell's Palsy; radiculopathy; herpes zoster; migraine; muscle weakness; hypesthesia; encephalitis

Skin and Subcutaneous Disorders

Stevens-Johnson syndrome; alopecia; petechiae; eczema

Musculoskeletal and Connective Tissue Disorders

Arthritis
Pain in extremity

Blood and Lymphatic System Disorders

Increased erythrocyte sedimentation rate; thrombocytopenia

Psychiatric Disorders

Irritability; agitation; somnolence

Eye Disorders

Optic neuritis; tinnitus; conjunctivitis; visual disturbances; uveitis

Cardiac Disorders

Syncope; tachycardia

The following adverse reaction has been reported with another Hepatitis B Vaccine (Recombinant) but not with RECOMBIVAX HB: keratitis.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

Do not mix RECOMBIVAX HB with any other vaccine in the same syringe or vial. Use separate injection sites and syringes for each vaccine.

In clinical trials in children, RECOMBIVAX HB was concomitantly administered with one or more of the following US licensed vaccines: Diphtheria, Tetanus and whole cell Pertussis; oral Poliomyelitis vaccine; Measles, Mumps, and Rubella Virus Vaccine, Live; Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] or a booster dose of Diphtheria, Tetanus, acellular Pertussis. Safety and immunogenicity were similar for concomitantly administered vaccines compared to separately administered vaccines.

In another clinical trial, a related HBsAg-containing product, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combination product (no longer licensed), was given concomitantly with eIPV (enhanced inactivated Poliovirus vaccine) or VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], using separate sites and syringes for injectable vaccines. No serious vaccine-related adverse events were reported, and no impairment of immune response to these individually tested vaccine antigens was demonstrated.

The Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combination product (no longer licensed) has also been administered concomitantly with the primary series of DTaP to a limited number of infants. No serious vaccine-related adverse events were reported.

7.2 Concomitant Administration with Immune Globulin

RECOMBIVAX HB may be administered concomitantly with HBIG. The first dose of RECOMBIVAX HB may be given at the same time as HBIG, but the injections should be administered at different sites.

7.3 Interference with Laboratory Tests

Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of a hepatitis B vaccine, including RECOMBIVAX HB.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively.

There are no adequate and well-controlled studies designed to evaluate RECOMBIVAX HB in pregnant women. Available post-approval data do not suggest an increased risk of miscarriage or major birth defects in women who received RECOMBIVAX HB during pregnancy.

Developmental toxicity studies have not been conducted with the vaccine in animals.

Data

Human Data

In post-licensure clinical studies of RECOMBIVAX HB, 26 pregnant women were inadvertently administered RECOMBIVAX HB following their last menstrual period. Among these pregnancies, after excluding elective terminations (n=3), there were 23 pregnancies with known outcomes all with exposure in the first trimester. Miscarriage was reported in 4 of 23 (17%) pregnancies and major birth defects were reported in 0 of 19 (0%) live births. The rates of miscarriage and major birth defects were consistent with estimated background rates.

Post-approval adverse reactions are reported voluntarily from a population of uncertain size. It is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

In prospectively reported spontaneous post-approval reports from 1986 to 2018, 105 women with known pregnancy outcomes were exposed to RECOMBIVAX HB during pregnancy following the last menstrual period. After excluding induced abortions (n=5), those with exposure in the third trimester (n=4), and those with an unknown exposure timing (n=6), there were 90 pregnancies with known outcomes with exposures in the first or second trimester. Miscarriage was reported for 7 of 90 (7.8%) pregnancies. Major birth defects were reported for 2 of 83 (2.4%) live born infants. The rates of miscarriage and major birth defects were consistent with estimated background rates.

8.2 Lactation

Risk Summary

It is not known whether RECOMBIVAX HB is excreted in human milk. Data are not available to assess the effects of RECOMBIVAX HB on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RECOMBIVAX HB and any potential adverse effects on the breastfed child from RECOMBIVAX HB or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to the disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of RECOMBIVAX HB have been established in all pediatric age groups. Maternally transferred antibodies do not interfere with the active immune response to the vaccine. *[See Adverse Reactions (6.1) and Clinical Studies (14.1 and 14.2).]* The safety and effectiveness of RECOMBIVAX HB Dialysis Formulation in children have not been established.

8.5 Geriatric Use

Clinical studies of RECOMBIVAX HB used for licensure did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. However, in later studies it has been shown that a diminished antibody response can be expected in persons older than 60 years of age.

11 DESCRIPTION

RECOMBIVAX HB Hepatitis B Vaccine (Recombinant) is a sterile suspension of non-infectious subunit viral vaccine derived from HBsAg produced in yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories.

The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The fermentation process involves growth of *Saccharomyces cerevisiae* on a complex fermentation medium which consists of an extract of yeast, soy peptone, dextrose, amino acids and mineral salts. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The purified protein is treated in phosphate buffer with formaldehyde and then coprecipitated with alum (potassium aluminum sulfate) to form bulk vaccine adjuvanted with amorphous aluminum hydroxyphosphate sulfate. Each dose contains less than 1% yeast protein. The vaccine produced by the Merck method has been shown to be comparable to the plasma-derived vaccine in terms of animal potency (mouse, monkey, and chimpanzee) and protective efficacy (chimpanzee and human).

The vaccine against hepatitis B, prepared from recombinant yeast cultures, is free of association with human blood or blood products.

RECOMBIVAX HB Hepatitis B Vaccine (Recombinant) is supplied in three formulations. *[See How Supplied/Storage and Handling (16).]*

Pediatric/Adolescent Formulation (Without Preservative), 10 mcg/mL: each 0.5 mL dose contains 5 mcg of hepatitis B surface antigen.

Adult Formulation (Without Preservative), 10 mcg/mL: each 1 mL dose contains 10 mcg of hepatitis B surface antigen.

Dialysis Formulation (Without Preservative), 40 mcg/mL: each 1 mL dose contains 40 mcg of hepatitis B surface antigen.

All formulations contain approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate, previously referred to as aluminum hydroxide) per mL of vaccine. In each formulation, hepatitis B surface antigen is adsorbed onto approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate) per mL of vaccine. The vaccine contains <15 mcg/mL residual formaldehyde. The vaccine is of the *adw* subtype.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

RECOMBIVAX HB has been shown to elicit antibodies to hepatitis B virus as measured by ELISA.

Antibody concentrations ≥10mIU/mL against HBsAg are recognized as conferring protection against hepatitis B infection.{2}

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

RECOMBIVAX HB has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility *[see Use in Specific Populations (8)]*.

14 CLINICAL STUDIES

14.1 Efficacy in Neonates with Peripartum Exposure to Hepatitis B

The protective efficacy of three 5 mcg doses of RECOMBIVAX HB has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg (a core-associated antigenic complex which correlates with high infectivity). In a clinical study of infants who received one dose of HBIG at birth followed by the recommended three-dose regimen of RECOMBIVAX HB, chronic infection had not occurred in 96% of 130 infants after nine months of follow-up.{4} The estimated efficacy in prevention of chronic hepatitis B infection was 95% as compared to the infection rate in untreated historical controls.{5} Significantly fewer neonates became chronically infected when given one dose of HBIG at birth followed by the recommended three-dose regimen of RECOMBIVAX HB when compared to historical controls who received only a single dose of HBIG.{6} As demonstrated in the above study, HBIG, when administered simultaneously with RECOMBIVAX HB at separate body sites, did not interfere with the induction of protective antibodies against hepatitis B virus elicited by the vaccine.{6}

14.2 Immunogenicity of a Three-Dose Regimen in Healthy Infants, Children, and Adolescents

Three 5 mcg doses of RECOMBIVAX HB induced a protective level of antibody in 100% of 92 infants, 99% of 129 children, and in 99% of 112 adolescents *[see Dosage and Administration (2.3)].*

14.3 Immunogenicity of a Two-Dose Regimen in Healthy Adolescents 11 through 15 Years of Age

For adolescents (11 through 15 years of age), the immunogenicity of a two-dose regimen (10 mcg at 0 and 4-6 months) was compared with that of the standard three-dose regimen (5 mcg at 0, 1, and 6 months) in an open, randomized, multicenter study. The proportion of adolescents receiving the two-dose regimen who developed a protective level of antibody one month after the last dose (99% of 255 subjects) appears similar to that among adolescents who received the three-dose regimen (98% of 121 subjects). After adolescents (11 through 15 years of age) received the first 10-mcg dose of the two-dose regimen, the proportion who developed a protective level of antibody was approximately 72%.

14.4 Immunogenicity in Healthy Adults

Clinical studies have shown that RECOMBIVAX HB when injected into the deltoid muscle induced protective levels of antibody in 96% of 1213 healthy adults who received the recommended three-dose regimen. Antibody responses varied with age; a protective level of antibody was induced in 98% of 787 young adults 20-29 years of age, 94% of 249 adults 30-39 years of age and in 89% of 177 adults ≥40 years of age.

14.5 Efficacy and Immunogenicity in Specific Populations

Chronic Hepatitis C Infection

In one published study, the seroprotection rates in individuals with chronic hepatitis C virus (HCV) infection given the standard regimen of RECOMBIVAX HB was approximately 70%.{7} In a second published study of intravenous drug users given an accelerated schedule of RECOMBIVAX HB, infection with HCV did not affect the response to RECOMBIVAX HB.{8}

Predialysis and Dialysis Adult Patients

Predialysis and dialysis adult patients respond less well to hepatitis B vaccines than do healthy individuals; however, vaccination of adult patients early in the course of their renal disease produces higher seroconversion rates than vaccination after dialysis has been initiated.{9} In addition, the responses to these vaccines may be lower if the vaccine is administered as a buttock injection. When 40 mcg of Hepatitis B Vaccine (Recombinant), was administered in the deltoid muscle, 89% of 28 participants developed anti-HBs with 86% achieving levels ≥10 mIU/mL. However, when the same dosage of this vaccine was administered inappropriately either in the buttock or a combination of buttock and deltoid, 62% of 47 participants developed anti-HBs with 55% achieving levels of ≥10 mIU/mL.

15 REFERENCES

1. CDC. A Comprehensive Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part I: Immunization of Infants, Children and Adolescents. MMWR Recommendations and Reports 2005; 54(RR16): 1-23. Appendix C - Postexposure Prophylaxis of

Persons with Discrete Identifiable Exposures to Hepatitis B Virus (HBV) and http://www.cdc.gov/hepatitis/hbv/pdfs/correctedtable4.pdf

2. CDC. Suboptimal Response to Hepatitis B Vaccine given by Injection into the Buttock. MMWR Weekly Report 1985; 34: 105-8, 113.
3. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 2: Immunization of Adults, MMWR 2006, *55*(RR-16): 1-25.
4. Stevens, C.E.; Taylor, P.E.; Tong, M.J., et al.: Prevention of Perinatal Hepatitis B Virus Infection with Hepatitis B Immune Globulin and Hepatitis B Vaccine, in Zuckerman, A.J. (ed.), "Viral Hepatitis and Liver Diseases", Alan R. Liss, 982-983, 1988.
5. Stevens, C.E.; Taylor, P.E.; Tong, M.J., et al.: Yeast-Recombinant Hepatitis B Vaccine, Efficacy with Hepatitis B Immune Globulin in Prevention of Perinatal Hepatitis B Virus Transmission, JAMA *257*(19): 2612-2616, 1987.
6. Beasley, R.P.; Hwang, L.; Stevens, C.E.; Lin, C.; Hsieh, F.; Wang, K.; Sun, T.; Szmuness, W.: Efficacy of Hepatitis B Immune Globulin for Prevention of Perinatal Transmission of the Hepatitis B Virus Carrier State: Final Report of a Randomized Double-Blind, Placebo-Controlled Trial, Hepatology *3:* 135-141, 1983.
7. Wiedmann, M.; Liebert, U.G.; Oesen, U.; Porst, H.; Wiese, M.; Schroeder, S.; Halm, U.; Mossner, J.; Berr, F.: Decreased Immunogenicity of Recombinant Hepatitis B Vaccine in Chronic Hepatitis C, Hepatology, *31:* 230-234, 2000.
8. Minniti, F.; Baldo, V.; Trivello, R.; Bricolo, R.; Di Furia, L.; Renzulli, G.; Chiaramonte, M.: Response to HBV vaccine in Relation to anti-HCV and anti-HBc Positivity: a Study in Intravenous Drug Addicts, Vaccine, *17:* 3083-3085, 1999.
9. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Hepatitis B Virus Infection: A Comprehensive Strategy to Eliminate Transmission in the United States, 1996 update, MMWR (draft January 13, 1996).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RECOMBIVAX HB (pediatric and adult) FORMULATION is available in single-dose vials and prefilled Luer-Lok® syringes.

RECOMBIVAX HB DIALYSIS FORMULATION is available in single-dose vials.

Pediatric/Adolescent Formulation (PRESERVATIVE FREE)

0.5 mL (5 mcg) in single-dose vials and prefilled Luer-Lok® syringes

NDC 0006-4981-00 – box of ten 0.5-mL single-dose vials

Color coded with a yellow cap and stripe on the vial labels and cartons and an orange banner on the vial labels and cartons

NDC 0006-4093-02 – carton of 10 prefilled single-dose Luer-Lok® syringes with tip caps

Color coded with a yellow plunger rod

Adult Formulation *(PRESERVATIVE FREE)*

1 mL (10mcg) in single-dose vials and prefilled Luer-Lok® syringes

NDC 0006-4995-00 – 1-mL single dose vial

Color coded with a green cap and stripe

NDC 0006-4995-41 – box of ten 1-mL single-dose vials

Color coded with a green cap and stripe

NDC 0006-4094-02 – carton of 10 pre-filled single-dose syringes with tip caps

Color coded with a green plunger rod

RECOMBIVAX HB DIALYSIS FORMULATION

1 mL (40mcg) in single-dose vials

NDC 0006-4992-00 – 1-mL single-dose vial

Color coded with a blue cap and stripe

16.2 Storage and Handling

- Protect from light.
- Store vials and syringes at 2-8°C (36-46°F).
- *Do not freeze since freezing destroys potency*.
- RECOMBIVAX HB is stable at temperatures from 0° to 25° C (32° to 75°F) for 72 hours. These data are not recommendations for shipping or storage but may guide decisions for use in case of temporary temperature excursions.

17 PATIENT COUNSELING INFORMATION

Information for Vaccine Recipients and Parents/Guardians

- Inform the patient, parent or guardian of the potential benefits and risks associated with vaccination, as well as the importance of completing the immunization series.
- Question the vaccine recipient, parent or guardian about the occurrence of any symptoms and/or signs of adverse reaction after a previous dose of hepatitis B vaccine.
- Tell the patient, parent or guardian to report adverse events to the physician or clinic where the vaccine was administered.
- Prior to vaccination, give the patient, parent or guardian the Vaccine Information Statements which are required by the National Vaccine Injury Act of 1986. The materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Tell the patient, parent or guardian that the United States Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events by the National Childhood Vaccine Injury Act of 1986. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at (www.vaers.hhs.gov).

Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of **MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-v232-i-1812r440

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENGERIX-B safely and effectively. See full prescribing information for ENGERIX-B.

ENGERIX-B [Hepatitis B Vaccine (Recombinant)] injectable suspension, for intramuscular use
Initial U.S. Approval: 1989

---------- INDICATIONS AND USAGE----------
ENGERIX-B is a vaccine indicated for immunization against infection caused by all known subtypes of hepatitis B virus. (1)

----------DOSAGE AND ADMINISTRATION----------
For intramuscular administration. (2, 2.2)
- Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Persons 20 years of age and older: A series of 3 doses (1 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Adults on hemodialysis: A series of 4 doses (2 mL each) as a single 2-mL dose or as two 1-mL doses on a 0-, 1-, 2-, 6-month schedule. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
ENGERIX-B is a sterile suspension available in the following presentations:
- 0.5-mL (10 mcg) single-dose vials and prefilled syringes (3)
- 1-mL (20 mcg) single-dose vials and prefilled syringes (3)

---------- CONTRAINDICATIONS ----------
Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)
- Temporarily defer vaccination of infants with a birth weight less than 2,000 g born to hepatitis B surface antigen (HBsAg)-negative mothers. (5.3)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. (5.4)

---------- ADVERSE REACTIONS ----------
The most common solicited adverse reactions were injection-site soreness (22%) and fatigue (14%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- DRUG INTERACTIONS----------
Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
- Antibody responses are lower in persons older than 60 years than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENGERIX-B is indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration. See Section 2.2 for subcutaneous administration in persons at risk of hemorrhage.

2.1 Preparation for Administration

Shake well before use. With thorough agitation, ENGERIX-B is a homogeneous, turbid white suspension. Do not administer if it appears otherwise. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the vaccine dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

2.2 Administration

ENGERIX-B should be administered by intramuscular injection. The preferred administration site is the anterolateral aspect of the thigh for infants younger than 1 year and the deltoid muscle in older children (whose deltoid is large enough for an intramuscular injection) and adults. ENGERIX-B should not be administered in the gluteal region; such injections may result in suboptimal response.

ENGERIX-B may be administered subcutaneously to persons at risk of hemorrhage (e.g., hemophiliacs). However, hepatitis B vaccines administered subcutaneously are known to result in a lower antibody response. Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons who are at risk of hemorrhage with intramuscular injections.

Do not administer this product intravenously or intradermally.

2.3 Recommended Dose and Schedule

Persons from Birth through 19 Years

Primary immunization for infants (born of hepatitis B surface antigen [HBsAg]-negative or HBsAg-positive mothers), children (birth through 10 years), and adolescents (aged 11 through 19 years) consists of a series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule.

Persons Aged 20 Years and Older

Primary immunization for persons aged 20 years and older consists of a series of 3 doses (1 mL each) given on a 0-, 1-, and 6-month schedule.

Adults on Hemodialysis

Primary immunization consists of a series of 4 doses (2-mL each) given as a single 2-mL dose or two 1-mL doses on a 0-, 1-, 2-, and 6-month schedule. In hemodialysis patients, antibody response is lower than in healthy persons and protection may persist only as long as antibody levels remain above 10 mIU/mL. Therefore, the need for booster doses should be assessed by annual antibody testing. A 2-mL booster dose (as a single 2-mL dose or two 1-mL doses) should be given when antibody levels decline below 10 mIU/mL.[1] *[See Clinical Studies (14.2).]*

Table 1. Recommended Dosage and Administration Schedules

Group	Dose[a]	Schedules
Infants born of:		
HBsAg-negative mothers	0.5 mL	0, 1, 6 months
HBsAg-positive mothers[b]	0.5 mL	0, 1, 6 months
Children:		
Birth through 10 years	0.5 mL	0, 1, 6 months
Adolescents:		
Aged 11 through 19 years	0.5 mL	0, 1, 6 months
Adults:		
Aged 20 years and older	1 mL	0, 1, 6 months
Adults on hemodialysis	2 mL[c]	0, 1, 2, 6 months

HBsAg = Hepatitis B surface antigen.

[a] 0.5 mL (10 mcg); 1 mL (20 mcg).

[b] Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth *[see Dosage and Administration (2.6)]*.

[c] Given as a single 2-mL dose or as two 1-mL doses.

2.4 Alternate Dosing Schedules

There are alternate dosing and administration schedules which may be used for specific populations (e.g., neonates born of hepatitis B–infected mothers, persons who have or might have been recently exposed to the virus, and travelers to high-risk areas) (Table 2). For some of these alternate schedules, an additional dose at 12 months is recommended for prolonged maintenance of protective titers.

Table 2. Alternate Dosage and Administration Schedules

Group	Dose[a]	Schedules
Infants born of:		
HBsAg-positive mothers[b]	0.5 mL	0, 1, 2, 12 months
Children:		
Birth through 10 years	0.5 mL	0, 1, 2, 12 months
Aged 5 through 10 years	0.5 mL	0, 12, 24 months[c]
Adolescents:		
Aged 11 through 16 years	0.5 mL	0, 12, 24 months[c]
Aged 11 through 19 years	1 mL	0, 1, 6 months
Aged 11 through 19 years	1 mL	0, 1, 2, 12 months
Adults:		
Aged 20 years and older	1 mL	0, 1, 2, 12 months

HBsAg = Hepatitis B surface antigen.

[a] 0.5 mL (10 mcg); 1 mL (20 mcg).

[b] Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth *[see Dosage and Administration (2.6)]*.

[c] For children and adolescents for whom an extended administration schedule is acceptable based on risk of exposure.

2.5 Booster Vaccinations

Whenever administration of a booster dose is appropriate, the dose of ENGERIX-B is 0.5 mL for children aged 10 years and younger and 1 mL for persons aged 11 years and older. Studies have demonstrated a substantial increase in antibody titers after booster vaccination with ENGERIX-B. See Section 2.3 for information on booster vaccination for adults on hemodialysis.

2.6 Known or Presumed Exposure to Hepatitis B Virus

Persons with known or presumed exposure to the hepatitis B virus (e.g., neonates born of infected mothers, persons who experienced percutaneous or permucosal exposure to the virus) should be given hepatitis B immune globulin (HBIG) in addition to ENGERIX-B in accordance with Advisory Committee on Immunization Practices recommendations and with the package insert for HBIG. ENGERIX-B can be given on either dosing schedule (0, 1, and 6 months or 0, 1, 2, and 12 months).

3 DOSAGE FORMS AND STRENGTHS

ENGERIX-B is a sterile suspension available in the following presentations:

- 0.5-mL (10 mcg) single-dose vials and prefilled TIP-LOK syringes
- 1-mL (20 mcg) single-dose vials and prefilled TIP-LOK syringes

[See Description (11), How Supplied/Storage and Handling (16).]

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast, is a contraindication to administration of ENGERIX-B *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Infants Weighing Less than 2,000 g at Birth

Hepatitis B vaccine should be deferred for infants with a birth weight <2,000 g if the mother is documented to be HBsAg negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or hospital discharge. Infants born weighing <2,000 g to HBsAg-positive mothers should receive vaccine and HBIG within 12 hours after birth. Infants born weighing <2,000 g to mothers of unknown HBsAg status should receive vaccine and HBIG within 12 hours after birth if the mother's HBsAg status cannot be determined within the first 12 hours of life. The birth dose in infants born weighing <2,000 g should not be counted as the first dose in the vaccine series and it should be followed with a full 3-dose standard regimen (total of 4 doses).[2] *[See Dosage and Administration (2).]*

5.4 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. For ENGERIX-B, this assessment should include consideration of the mother's hepatitis B antigen status and the high probability of maternal transmission of hepatitis B virus to infants born of mothers who are HBsAg positive if vaccination is delayed.

5.5 Preventing and Managing Allergic Vaccine Reactions

Prior to immunization, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of

immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur. *[See Contraindications (4).]*

5.6 Moderate or Severe Acute Illness

To avoid diagnostic confusion between manifestations of an acute illness and possible vaccine adverse effects, vaccination with ENGERIX-B should be postponed in persons with moderate or severe acute febrile illness unless they are at immediate risk of hepatitis B infection (e.g., infants born of HBsAg-positive mothers).

5.7 Altered Immunocompetence

Immunocompromised persons may have a diminished immune response to ENGERIX-B, including individuals receiving immunosuppressant therapy.

5.8 Multiple Sclerosis

Results from 2 clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis,[3] and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.[4]

5.9 Limitations of Vaccine Effectiveness

Hepatitis B has a long incubation period. ENGERIX-B may not prevent hepatitis B infection in individuals who had an unrecognized hepatitis B infection at the time of vaccine administration. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The most common solicited adverse reactions were injection site soreness (22%) and fatigue (14%).

In 36 clinical studies, a total of 13,495 doses of ENGERIX-B were administered to 5,071 healthy adults and children who were initially seronegative for hepatitis B markers, and healthy neonates. All subjects were monitored for 4 days post-administration. Frequency of adverse reactions tended to decrease with successive doses of ENGERIX-B.

Using a symptom checklist, the most frequently reported adverse reactions were injection site soreness (22%) and fatigue (14%). Other reactions are listed below. Parent or guardian completed forms for children and neonates. Neonatal checklist did not include headache, fatigue, or dizziness.

Incidence 1% to 10% of Injections

Nervous System Disorders: Dizziness, headache.

General Disorders and Administration Site Conditions: Fever (>37.5°C), injection site erythema, injection site induration, injection site swelling.

Incidence <1% of Injections

Infections and Infestations: Upper respiratory tract illnesses.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Agitation, insomnia.

Nervous System Disorders: Somnolence, tingling.

Vascular Disorders: Flushing, hypotension.

Gastrointestinal Disorders: Abdominal pain/cramps, constipation, diarrhea, nausea, vomiting.

Skin and Subcutaneous Tissue Disorders: Erythema, petechiae, pruritus, rash, sweating, urticaria.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, myalgia, pain/stiffness in arm, shoulder, or neck.

General Disorders and Administration Site Conditions: Chills, influenza-like symptoms, injection site ecchymosis, injection site pain, injection site pruritus, irritability, malaise, weakness.

In a clinical trial, 416 adults with type 2 diabetes and 258 control subjects without type 2 diabetes who were seronegative for hepatitis B markers received at least 1 dose of ENGERIX-B. Subjects were monitored for solicited adverse reactions for 4 days following each vaccination. The most frequently reported solicited adverse reactions in the entire study population were injection site pain (reported in 39% of diabetic subjects and 45% of control subjects) and fatigue (reported in 29% of diabetic subjects and 27% of control subjects). Serious adverse events were monitored through 30 days following the last vaccination. Serious adverse events (SAEs) occurred in 3.8% of diabetic subjects and 1.6% of controls. No SAEs were deemed related to ENGERIX-B.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ENGERIX-B. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Infections and Infestations

Herpes zoster, meningitis.

Blood and Lymphatic System Disorders

Thrombocytopenia.

Immune System Disorders

Allergic reaction, anaphylactoid reaction, anaphylaxis. An apparent hypersensitivity syndrome (serum sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as urticaria, erythema multiforme, ecchymoses, and erythema nodosum.

Nervous System Disorders

Encephalitis; encephalopathy; migraine; multiple sclerosis; neuritis; neuropathy including hypoesthesia, paresthesia, Guillain-Barré syndrome and Bell's palsy; optic neuritis; paralysis; paresis; seizures; syncope; transverse myelitis.

Eye Disorders

Conjunctivitis, keratitis, visual disturbances.

Ear and Labyrinth Disorders

Earache, tinnitus, vertigo.

Cardiac Disorders

Palpitations, tachycardia.

Vascular Disorders

Vasculitis.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, bronchospasm including asthma-like symptoms.

Gastrointestinal Disorders

Dyspepsia.

Skin and Subcutaneous Tissue Disorders

Alopecia, angioedema, eczema, erythema multiforme including Stevens-Johnson syndrome, erythema nodosum, lichen planus, purpura.

Musculoskeletal and Connective Tissue Disorders

Arthritis, muscular weakness.

General Disorders and Administration Site Conditions

Injection site reaction.

Investigations

Abnormal liver function tests.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Vaccines and Immune Globulin

ENGERIX-B may be administered concomitantly with immune globulin.

When concomitant administration of other vaccines or immune globulin is required, they should be given with different syringes and at different injection sites. Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial.

7.2 Interference with Laboratory Tests

HBsAg derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of a hepatitis B vaccine, including ENGERIX-B.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no adequate and well-controlled studies of ENGERIX-B in pregnant women in the U.S. Available data do not suggest an increased risk of major birth defects and miscarriage in women who received ENGERIX-B during pregnancy *(see Data)*.

There are no animal studies with ENGERIX-B to inform use during pregnancy. A developmental toxicity study was performed in female rats administered a vaccine with the same hepatitis B surface antigen component and quantity as ENGERIX-B prior to mating and during gestation (0.2 mL at each occasion). This study revealed no adverse effects on fetal or pre-weaning development (*see Data*).

Data

Human Data: In an evaluation of pre- and post-licensure clinical trials of ENGERIX-B, 58 pregnant women were inadvertently administered ENGERIX-B following their last menstrual period. After excluding elective terminations (n = 6), those with an unknown outcome (n = 3), those with exposure in the third trimester (n = 1), and those with an unknown exposure timing

(n = 22), there were 26 pregnancies with known outcomes with exposure in the first or second trimester. Miscarriage was reported in 11.5% of pregnancies with exposure prior to 20 weeks of gestation (3/26) and major birth defects were reported in 0% (0/23) of live births born to women with exposure during the first or second trimester. The rates of miscarriage and major birth defects were consistent with estimated background rates.

No pregnancy registry for ENGERIX-B was conducted. TWINRIX [Hepatitis A & Hepatitis B (Recombinant) Vaccine] is a bivalent vaccine containing the same hepatitis B surface antigen component and quantity as used in ENGERIX-B. Therefore, clinical data accrued with TWINRIX are relevant to ENGERIX-B. A pregnancy exposure registry was maintained for TWINRIX from 2001 to 2015. The registry prospectively enrolled 245 women who received a dose of TWINRIX during pregnancy or within 28 days prior to conception. After excluding induced abortions (n = 6, including one of a fetus with congenital anomalies), those lost to follow-up (n = 142), those with exposure in the third trimester (n = 1), and those with an unknown exposure timing (n = 9), there were 87 pregnancies with known outcomes with exposure within 28 days prior to conception, or in the first or second trimesters. Miscarriage was reported for 9.6% of pregnancies with exposure to TWINRIX prior to 20 weeks gestation (8/83). Major birth defects were reported for 3.8% of live born infants whose mothers were exposed within 28 days prior to conception or during the first or second trimester (3/80). The rates of miscarriage and major birth defects were consistent with estimated background rates.

Animal Data: In a developmental toxicity study, female rats were administered TWINRIX, which contains the same hepatitis B surface antigen component and quantity as ENGERIX-B, by intramuscular injection on Day 30 prior to mating and on gestation Days 6, 8, 11, and 15. The total dose was 0.2 mL (divided) at each occasion (a single human dose is 1 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no fetal malformations or variations.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ENGERIX-B in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENGERIX-B and any potential adverse effects on the breastfed child from ENGERIX-B or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of ENGERIX-B have been established in all pediatric age-groups. Maternally transferred antibodies do not interfere with the active immune response to the vaccine. *[See Adverse Reactions (6), Clinical Studies (14.1, 14.3, 14.4).]*

The timing of the first dose in infants weighing less than 2,000 g at birth depends on the HBsAg status of the mother. *[See Warnings and Precautions (5.3).]*

8.5 Geriatric Use

Clinical studies of ENGERIX-B used for licensure did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. However, in later studies it has been shown that a diminished antibody response and seroprotective levels can be expected in persons older than 60 years.[5] *[See Clinical Studies (14.2).]*

11 DESCRIPTION

ENGERIX-B [Hepatitis B Vaccine (Recombinant)] is a sterile suspension of noninfectious HBsAg for intramuscular administration. It contains purified surface antigen of the virus obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus. The HBsAg expressed in the cells is purified by several physicochemical steps and formulated as a suspension of the antigen adsorbed on aluminum hydroxide. The procedures used to manufacture ENGERIX-B result in a product that contains no more than 5% yeast protein.

Each 0.5-mL pediatric/adolescent dose contains 10 mcg of HBsAg adsorbed on 0.25 mg aluminum as aluminum hydroxide.

Each 1-mL adult dose contains 20 mcg of HBsAg adsorbed on 0.5 mg aluminum as aluminum hydroxide.

ENGERIX-B contains the following excipients: Sodium chloride (9 mg/mL) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).

ENGERIX-B is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

ENGERIX-B is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.[1] Seroconversion is defined as antibody titers ≥1 mIU/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ENGERIX-B has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Vaccination of female rats with TWINRIX, which contains the same HBsAg component and quantity as ENGERIX-B, had no effect on fertility. *[See Use in Specific Populations (8.1).]*

14 CLINICAL STUDIES

14.1 Efficacy in Neonates

Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at high risk of hepatitis B infection.[6,7] Fifty-eight neonates born of mothers who were both HBsAg-positive and hepatitis B "e" antigen (HBeAg)-positive were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 2 months, without concomitant hepatitis B immune globulin (HBIG). Two infants became chronic carriers in the 12-month follow-up period after initial inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the chronic carrier state during the first 12 months of life was 95%.

14.2 Efficacy and Immunogenicity in Specific Populations

Homosexual Men

ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months was evaluated in homosexual men aged 16 to 59 years. Four of 244 subjects became infected with hepatitis B during the period prior to completion of the 3-dose immunization schedule. No additional subjects became infected during the 18-month follow-up period after completion of the immunization course.

Adults with Chronic Hepatitis C

In a clinical trial of 67 adults aged 25 to 67 years with chronic hepatitis C, ENGERIX-B (20 mcg/1 mL) was given at 0, 1, and 6 months. Of the subjects assessed at Month 7 (n = 31), 100% responded with seroprotective titers. The geometric mean antibody titer (GMT) was 1,260 mIU/mL (95% Confidence Interval [CI]: 709, 2,237).

Adults on Hemodialysis

Hemodialysis patients given hepatitis B vaccines respond with lower titers, which remain at protective levels for shorter durations than in normal subjects. In a clinical trial of 56 adults who had been on hemodialysis for a mean period of 56 months, ENGERIX-B (40 mcg/2 mL given as two 1-mL doses) was given at 0, 1, 2, and 6 months. Two months after the fourth dose, 67% (29/43) of patients had seroprotective antibody levels (≥10 mIU/mL) and the GMT among seroconverters was 93 mIU/mL.

Adults with Type 2 Diabetes Mellitus

In a descriptive study, 674 adult subjects with type 2 diabetes (diagnosed within the preceding 5 years) or without type 2 diabetes were enrolled and stratified by age and body mass index (BMI). The per-protocol immunogenicity cohort included 378 diabetic subjects and 189 matched control subjects who received ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months. Among these subjects, the mean age was 54 years (range: 20 to 82 years); mean BMI was 32 kg/m^2 (range: 17 to 64 kg/m^2); 51% were male; 88% were white, 3% were American Indian or Alaskan Native, 3% were black, 2% were Asian, 4% were other racial groups; 2% were Hispanic or Latino.

The overall seroprotection rates (1 month after the third dose) were 75% (95% CI: 71, 80) in patients with diabetes and 82% (95% CI: 76, 87) in control subjects. The seroprotection rates in those with diabetes aged 20 to 39 years, 40 to 49 years, 50 to 59 years, and at least 60 years were 89%, 81%, 83%, and 58%, respectively. The seroprotection rates in those without diabetes in these same age-groups were 100%, 86%, 82%, and 70%, respectively. Subjects with diabetes and a BMI of at least 30 kg/m^2 had a seroprotection rate of 72% compared with 80% in diabetic subjects with lower BMIs. In control subjects, seroprotection rates were 82% in those with a BMI of at least 30 kg/m^2 and 83% in those with lower BMIs.

14.3 Immunogenicity in Neonates

In clinical studies, neonates were given ENGERIX-B (10 mcg/0.5 mL) at age 0, 1, and 6 months or at age 0, 1, and 2 months. The immune response to vaccination was evaluated in sera obtained 1 month after the third dose of ENGERIX-B.

Among infants administered ENGERIX-B at age 0, 1, and 6 months, 100% of evaluable subjects (n = 52) seroconverted by Month 7. The GMT was 713 mIU/mL. Of these, 97% had seroprotective levels (≥10 mIU/mL).

Among infants enrolled (n = 381) to receive ENGERIX-B at age 0, 1, and 2 months, 96% had seroprotective levels (≥10 mIU/mL) by Month 4. The GMT among seroconverters (n = 311) (antibody titer ≥1 mIU/mL) was 210 mIU/mL. A subset of these children received a fourth dose of ENGERIX-B at age 12 months. One month following this dose, seroconverters (n = 126) had a GMT of 2,941 mIU/mL.

14.4 Immunogenicity in Children and Adults

Persons Aged 6 Months through 10 Years

In clinical trials, children (N = 242) aged 6 months through 10 years were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 6 months. One to 2 months after the third dose, the seroprotection rate was 98% and the GMT of seroconverters was 4,023 mIU/mL.

Persons Aged 5 through 16 Years

In a separate clinical trial including both children and adolescents aged 5 through 16 years, ENGERIX-B (10 mcg/0.5 mL) was administered at 0, 1, and 6 months (n = 181) or 0, 12, and

24 months (n = 161). Immediately before the third dose of vaccine, seroprotection was achieved in 92.3% of subjects vaccinated on the 0-, 1-, and 6-month schedule and 88.8% of subjects on the 0-, 12-, and 24-month schedule (GMT: 118 mIU/mL versus 162 mIU/mL, respectively, $P = 0.18$). One month following the third dose, seroprotection was achieved in 99.5% of children vaccinated on the 0-, 1-, and 6-month schedule compared with 98.1% of those on the 0-, 12-, and 24-month schedule. GMTs were higher ($P = 0.02$) for children receiving vaccine on the 0-, 1-, and 6-month schedule compared with those on the 0-, 12-, and 24-month schedule (5,687 mIU/mL versus 3,159 mIU/mL, respectively).

Persons Aged 11 through 19 Years

In clinical trials with healthy adolescent subjects aged 11 through 19 years, ENGERIX-B (10 mcg/0.5 mL) given at 0, 1, and 6 months produced a seroprotection rate of 97% at Month 8 (n = 119) with a GMT of 1,989 mIU/mL (n = 118, 95% CI: 1,318, 3,020). Immunization with ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months produced a seroprotection rate of 99% at Month 8 (n = 122) with a GMT of 7,672 mIU/mL (n = 122, 95% CI: 5,248, 10,965).

Persons Aged 16 through 65 Years

Clinical trials in healthy adult and adolescent subjects (aged 16 through 65 years) have shown that following a course of 3 doses of ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months, the seroprotection (antibody titers ≥10 mIU/mL) rate for all individuals was 79% at Month 6 (5 months after second dose) and 96% at Month 7 (1 month after third dose); the GMT for seroconverters was 2,204 mIU/mL at Month 7 (n = 110).

An alternate 3-dose schedule (20 mcg/1 mL given at 0, 1, and 2 months) designed for certain populations (e.g., individuals who have or might have been recently exposed to the virus and travelers to high-risk areas) was also evaluated. At Month 3 (1 month after third dose), 99% of all individuals were seroprotected and remained protected through Month 12. On the alternate schedule, a fourth dose of ENGERIX-B (20 mcg/1 mL) at 12 months produced a GMT of 9,163 mIU/mL at Month 13 (1 month after fourth dose) (n = 373).

Persons Aged 40 Years and Older

Among subjects aged 40 years and older given ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months, the seroprotection rate 1 month after the third dose was 88% and the GMT for seroconverters was 610 mIU/mL (n = 50). In adults aged older than 40 years, ENGERIX-B produced anti-HBsAg antibody titers that were lower than those in younger adults.

14.5 Interchangeability with Other Hepatitis B Vaccines

A controlled study (N = 48) demonstrated that completion of a course of immunization with 1 dose of ENGERIX-B (20 mcg/1 mL) at Month 6 following 2 doses of RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant)] (10 mcg) at Months 0 and 1 produced a similar GMT (4,077 mIU/mL) to immunization with 3 doses of RECOMBIVAX HB (10 mcg) at Months 0, 1,

and 6 (GMT: 2,654 mIU/mL). Thus, ENGERIX-B can be used to complete a vaccination course initiated with RECOMBIVAX HB.[8]

15 REFERENCES

1. Centers for Disease Control and Prevention. Hepatitis B. In: Atkinson W, Wolfe C, Humiston S, Nelson R, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* 6th ed. Atlanta, GA: Public Health Foundation; 2000:207-229.
2. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: Immunization of Infants, Children, and Adolescents, *MMWR.* 2005;54(RR-16):1-23.
3. Ascherio A, Zhang SM, Hernán MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med.* 2001;344(5):327-332.
4. Confavreux C, Suissa S, Saddier P, et al. Vaccination and the risk of relapse in multiple sclerosis. *N Engl J Med.* 2001-344(5):319-326.
5. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 2: Immunization of Adults, *MMWR.* 2006;55(RR-16):1-25.
6. André FE, Safary A. Clinical experience with a yeast-derived hepatitis B vaccine. In: Zuckerman AJ, ed. *Viral Hepatitis and Liver Disease*. New York, NY: Alan R Liss, Inc.; 1988:1025-1030.
7. Poovorawan Y, Sanpavat S, Pongpunlert W, et al. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. *JAMA*. 1989;261(22):3278-3281.
8. Bush LM, Moonsammy GI, Boscia JA. Evaluation of initiating a hepatitis B vaccination schedule with one vaccine and completing it with another. *Vaccine*. 1991;9(11):807-809.

16 HOW SUPPLIED/STORAGE AND HANDLING

ENGERIX-B is available in single-dose vials and prefilled disposable TIP-LOK syringes (packaged without needles) (Preservative-Free Formulation):

10 mcg/0.5 mL Pediatric/Adolescent Dose

NDC 58160-820-01 Vial in Package of 10: NDC 58160-820-11

NDC 58160-820-43 Syringe in Package of 10: NDC 58160-820-52

20 mcg/mL Adult Dose

NDC 58160-821-01 Vial in Package of 10: NDC 58160-821-11

NDC 58160-821-05 Syringe in Package of 1: NDC 58160-821-34

NDC 58160-821-43 Syringe in Package of 10: NDC 58160-821-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been frozen. Do not dilute to administer.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients and parents or guardians of the potential benefits and risks of immunization with ENGERIX-B.
- Emphasize, when educating vaccine recipients and parents or guardians regarding potential side effects, that ENGERIX-B contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Instruct vaccine recipients and parents or guardians to report any adverse events to their healthcare provider.
- Give vaccine recipients and parents or guardians the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Manufactured by **GlaxoSmithKline Biologicals**
Rixensart, Belgium, U.S. License No. 1617
Distributed by **GlaxoSmithKline**
Research Triangle Park, NC 27709

ENG:XXPI

Footnote 16

From: Jones, Sarah (CDC/OID/NCEZID)
Sent: Wednesday, December 06, 2017 1:23 PM
To: Nguyen, Lyn (CDC/OID/NCEZID) <ivx1@cdc.gov>; Limeres, Alexa (CDC/OID/NCEZID) <vst6@cdc.gov>; Clasp, Samuel (CDC/OID/NCEZID) (CTR) <nss4@cdc.gov>; Goodman, Jeremy A. (CDC/OID/NCEZID) <vhj2@cdc.gov>
Cc: DHQP_Policy (CDC) <DHQP_Policy@cdc.gov>; Holmes, Carissa B. (CDC/OID/NCEZID) <ipz3@cdc.gov>; McMillen, Amy (CDC/OID/NCEZID) <auh1@cdc.gov>; Knights, Paulette (CDC/OID/NCEZID) <pbf7@cdc.gov>
Subject: FW: OASH clearance -- HHS Vaccine Safety Responsibilities and Notice Pursuant to 42 U.S. C.Â§ 300aa-31

Hi DHQP team,

Attached is a letter response to the Informed Consent Action Network on HHS vaccine safety and responsibilities.

Comments are due **by 10 a.m. Monday, Dec. 13.**

Thanks,

Sarah

From: Toye, Sally (CDC/OD/OCS)
Sent: Wednesday, December 6, 2017 1:13 PM
To: Swartwood, Candice (CDC/OID/NCIRD) <chj8@cdc.gov>; Beauvais, Denise (CDC/OID/NCIRD) <cry2@cdc.gov>; Jones, Sarah (CDC/OID/NCEZID) <nhd4@cdc.gov>; NCHHSTP Policy (CDC) <nchhstppolicy@cdc.gov>
Cc: CDC Review Clear Coordinator <rcc@cdc.gov>; Hoffmann, Lauren (CDC/OD/OCS) <cpf5@cdc.gov>; Clark, Cynthia K. (CDC/OD/OCS) <cfc8@cdc.gov>
Subject: OASH clearance -- HHS Vaccine Safety Responsibilities and Notice Pursuant to 42 U.S. C.Â§ 300aa-31

OS/ES assigned the attached letter to OASH for direct reply. The National Vaccine Program Office staff has pulled together a draft response and is requesting that it be cleared with CDC, OGC, FDA, HRSA, NIH, and AHRQ for review prior to signature.

Please send any comment by 10:00am on Monday Dec. 13th. Thanks!

NOV 0 7 2017

ICAN
Informed Consent Action Network

VIA FEDEX

November 6, 2017

U.S. Department of Health & Human Services
HHS Office of the Secretary
Eric D. Hargan
Acting Secretary of Health & Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *Correspondence Email Address*

Dear Secretary Hargan:

As a follow-up to our letter, dated October 12, 2017 (copy enclosed), any response to same should be sent via electronic mail to del@icandecide.com and cat@icandecide.com

Very truly yours,

Del Bigtree

Enclosure: *Copy of letter from Del Bigtree to Eric D. Hargan dated October 12, 2017*

ICAN
Informed Consent Action Network

VIA FEDEX

October 12, 2017

U.S. Department of Health & Human Services
HHS Office of the Secretary
Don Wright, M.D., M.P.H.
Acting Secretary of Health & Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *HHS Vaccine Safety Responsibilities and Notice Pursuant to 42 U.S.C. § 300aa-31*

Dear Secretary Wright:

Informed Consent Action Network hereby provides notice per 42 U.S.C. § 300aa-31(b).

Americans, including the over 55 organizations listed below, whose members exceed 5 million Americans, are concerned about vaccine safety. The National Childhood Vaccine Injury Act of 1986 (the **1986 Act**) made nearly every aspect of vaccine safety the exclusive responsibility of the Department of Health & Human Services (**HHS**). As the Secretary of HHS (the **Secretary**), this means you shoulder virtually all responsibility for assuring the safety of vaccines administered to America's 78 million children.

This notice respectfully requests confirmation that certain obligations regarding vaccine safety required under the 1986 Act have been fulfilled or will forthwith be fulfilled. These specific requests are numbered sequentially in this notice. We would welcome the opportunity to meet and discuss reasonable means for complying with these requests. If that is not possible, the 1986 Act authorizes "a civil action ... against the Secretary where there is alleged a failure of the Secretary to perform any act or duty" under the 1986 Act.

I. Background

The 1986 Act granted economic immunity to pharmaceutical companies for injuries caused by their vaccines. (42 U.S.C. § 300aa-11.) The 1986 Act thereby eliminated the market force which drives safety for all other products – actual and potential product liability. Recognizing the unprecedented elimination of this market force, the 1986 Act makes HHS directly responsible for virtually every aspect of vaccine safety. (42 U.S.C. §§ 300aa-2, 300aa-27.)

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: 12 Dec 2017 13:34:55 -0500
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Nguyen, Lyn (CDC/OID/NCEZID)
Subject: RE: Consolidated Response to ICAN_Del Bigtree V3_LN_FD-tts- version 2

I had a few very minor editorial changes that I sent back to Lyn earlier today. FDA and NVPO were okay with our language.

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Tuesday, December 12, 2017 1:33 PM
To: Nguyen, Lyn (CDC/OID/NCEZID) <ivx1@cdc.gov>; Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Subject: RE: Consolidated Response to ICAN_Del Bigtree V3_LN_FD-tts- version 2

I think it looks good. Thanks.

From: Nguyen, Lyn (CDC/OID/NCEZID)
Sent: Monday, December 11, 2017 5:37 PM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>; Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: Consolidated Response to ICAN_Del Bigtree V3_LN_FD-tts- version 2

Thank you again for walking me through the issues. Attached is the updated response to the areas we discussed. Let me know if you are OK with what we have and when you hear back from FDA.

-Lyn

Lyn Thi Nguyen, MPH
Public Health Analyst (Policy)
Division of Healthcare Quality Promotion/NCEZID
U.S. Centers for Disease Control and Prevention
1600 Clifton Road, MS A-07
Atlanta, GA 30329
(Tel) 404.639.7391
(BB) 404.386.3994
(Fax) 404-718-1900
(E-mail) ivx1@cdc.gov
Telework Mondays and Fridays - please contact by BB and e-mail

Footnote 17

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

JAN 18 2018

Mr. Del Bigtree
Informed Consent Action Network
10200 US HWY 290 W, Suite 301
Austin, Texas 78736

Dear Mr. Bigtree:

Acting Secretary Hargan has asked me to thank you for your letter expressing interest in vaccine safety and in and the federal policies guiding the licensing, recommendation, and safety monitoring of immunizations, and to respond to you directly.

The Department of Health and Human Services has a far-reaching mission to enhance and protect the health of all Americans. Vaccines are held to the highest standard of safety to both protect people from adverse reactions and enhance their health by preventing a number of serious diseases. I am proud to report that data show the United States currently has the safest supply in history.

I have provided responses to your specific questions in the enclosure to this letter. Thank you for the opportunity to address your concerns.

Sincerely yours,

Melinda Wharton

Melinda Wharton, MD, MPH
Acting Director, National Vaccine Program Office

Enclosure

HHS Responses to Questions and Comments from Mr. Bigtree

I would like to address a comment made in section II of your letter about pre-licensure safety review of pediatric vaccines. Contrary to statements made on page two of your letter, many pediatric vaccines have been investigated in clinical trials that included a placebo. In addition, there appears to be a misunderstanding regarding the term "solicited" adverse events. Typically, in vaccine trials, the incidence of certain specific clinical findings that might be expected after vaccination is monitored for a short period of time after vaccination. Because these events are pre-specified, they are considered to be "solicited" events. In addition, other unexpected or severe adverse events, which may occur over a longer period of time following vaccination, are also analyzed and evaluated by FDA, but because these events are not predicted prior to initiation of the study, these are not called "solicited" adverse events. Please be assured that vaccine safety is carefully examined regardless of whether there is a placebo included in the clinical trials. Once vaccines are approved, the safety is also carefully monitored, in some cases by manufacturer-conducted post-marketing studies by Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), or the Post-licensure Rapid Immunization Safety Monitoring System (PRISM), as well as other mechanisms.

(1) Please explain how HHS justifies licensing any pediatric vaccine without first conducting a long-term clinical trial in which the rate of adverse reactions is compared between the subject group and a control group receiving an inert placebo?

Inert placebo controls are not required to understand the safety profile of a new vaccine, and are thus not required. In some cases, inclusion of placebo control groups is considered unethical. Even in the absence of a placebo, control groups can be useful in evaluating whether the incidence of a specific observed adverse event exceeds that which would be expected without administration of the new vaccine. Serious adverse events are always carefully evaluated by FDA to determine potential association with vaccination regardless of their rate of incidence in the control group. In cases where an active control is used, the adverse event profile of that control group is usually known and the findings of the study are reviewed in the context of that knowledge.

(2) Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life?

Data relied upon in licensing infant use of hepatitis B vaccines is summarized in the respective package inserts. Furthermore, pediatric data from other countries and in the literature, support the safety of these vaccines in infants. The recommendation for all children to receive these vaccines was made by the Advisory Committee for

Immunization Practices. Their reasoning is summarized in a *Morbidity and Mortality Weekly Report* at https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm. Follow-up studies support the safety of infant vaccination with hepatitis B vaccines.

(3) Please explain why HHS failed to cooperate with Harvard to automate VAERS reporting? And detail any steps that HHS has taken since toward automating VAERS reporting?

On June 30, 2017, the Centers for Disease Control and Prevention (CDC) and FDA implemented a revised reporting form and a new process for submitting reports to the VAERS for non-manufacturer reports. Persons reporting adverse events are now able to use the VAERS 2.0 online reporting tool to submit reports directly online; alternatively, they may download and complete the writable and savable VAERS 2.0 form and submit it using an electronic document upload feature. Vaccine manufacturers submit VAERS reports electronically through the FDA Electronic Submissions Gateway (ESG). With VAERS 2.0 and the FDA ESG, multiple electronic options exist for VAERS reporting.

In addition, CDC is developing the next generation of spontaneous reporting mechanisms for the VAERS. Following its initial work with Harvard, CDC completed a successful proof of concept study with Harvard and other partners that takes advantage of electronic health records (EHR) and computer algorithms to facilitate direct reporting from EHR systems. You can read about that study at https://academic.oup.com/cid/article/61/6/864/451758. CDC continues to explore options to further develop this capability.

(4) Please explain any specific steps taken by HHS to improve adverse reaction reporting to VAERS?

Please see my response to question #3.

(5) For each of the 38 vaccine-injury pairs reviewed in the 1994 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please refer to the latest review of the "Safety of Vaccines Used for Routine Immunization in the United States" published in 2014 at https://www.ahrq.gov/research/findings/evidence-based-reports/vaccinestp.html. This report reviewed and accepted the findings of the 2011 Institute of Medicine report and provides an independent, systematic review of the literature published after that report on the safety of vaccines recommended for routine immunization of children, adolescents,

and adults in the United States. The report, highlighted in the July 2014 issue of *Pediatrics*, provides the most comprehensive review to date of published studies on the safety of routine vaccines recommended for children in the United States. The report concludes that the risk of rare adverse events must be weighed against the protective benefits that vaccines provide. Furthermore, the Centers for Disease Control and Prevention (CDC) has been working to address several of the vaccine-injury pairs that have been identified in the reports mentioned above. A list of CDC vaccine safety publications can be found at: https://www.cdc.gov/vaccinesafety/research/publications/index.html.

(6) For each of the 135 vaccine-injury pairs reviewed in the 2011 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please see response to question #5.

(7) Please explain what HHS has done to assure that health care providers record the manufacturer and lot number for each vaccine they administer?

Health care providers who administer vaccines covered by the National Vaccine Injury Compensation Program (VICP) are required under the National Childhood Vaccine Injury Act of 1986 (Vaccine Act), as amended, to ensure that the permanent medical record of the recipient (or a permanent office log or file) indicates the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine. This provision of the Vaccine Act applies to any vaccine for which there is a routine recommendation for childhood vaccination, even if many or most doses of the vaccine are administered to adults (e.g., influenza vaccine). In addition, the provider is required to record the edition date of the Vaccine Information Statement (VIS) distributed and the date those materials were provided.

The Advisory Committee on Immunization Practices (ACIP) also issued "General Best Practice Guidelines for Immunization" at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/records.html. This report provides information for clinicians and other health care providers about concerns that commonly arise when vaccinating persons of various ages, and includes a chapter on vaccination records that reinforces the Vaccine Act's requirement to record in the recipient's medical record (or a permanent office log or file) the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine.

(8) Please advise when HHS intends to begin conducting research to identify which children are susceptible to serious vaccine injury? If HHS believes it has commenced this research, please detail its activities regarding same?

HHS is currently supporting several initiatives that focus on advancing research on the fields of precision vaccinology (vaccine formulations tailored on the individual immune reactivity status) and adversomics (the study of vaccine adverse reactions using immunogenomics and systems biology approaches). Two examples are listed below:

- https://www.immuneprofiling.org/hipc/page/showPage?pg=about
- https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

(9) Please confirm that HHS shall forthwith remove the claim that "Vaccines Do Not Cause Autism" from the CDC website, or alternatively, please identify the specific studies on which HHS bases its blanket claim that no vaccines cause autism?

Vaccines are held to strict standards of safety. Many studies have looked at whether there is a relationship between vaccines and autism spectrum disorder (ASD). These studies continue to show that vaccines do **not** cause ASD. For more information, please refer to the literature below:

- https://www.cdc.gov/vaccinesafety/pdf/cdcstudiesonvaccinesandautism.pdf
- http://nationalacademies.org/hmd/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
- http://www.jpeds.com/article/S0022-3476(13)00144-3/pdf?ext=.pdf
  http://nationalacademies.org/HMD/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx

While there is still a lot to learn about ASD, research from public and private organizations indicate that environmental and genetic factors may increase the risk of autism, not vaccines or vaccine ingredients. HHS continues to research this issue to search for answers to better understand the risk factors and causes of this disease. Recent efforts to coordinate autism research are reflected in the "Strategic Plan for Autism Spectrum Disorder Research" by the Interagency Autism Coordinating Committee at https://iacc.hhs.gov/publications/strategic-plan/2017/.

(10) Please advise whether HHS intends to forthwith conduct adequately powered and controlled prospective as well as retrospective studies comparing total health outcomes of fully/partially vaccinated with completely unvaccinated children?

HHS tasked the Institute of Medicine (IOM) to identify research approaches, methodologies, and study designs that could address questions about the safety of the current schedule. This report is the most comprehensive examination of the immunization schedule to date and can be found at http://nationalacademies.org/HMD/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx. The IOM committee uncovered no evidence of major safety concerns associated with adherence to the childhood immunization schedule. The committee also cited ethical concerns about conducting a new study to compare the health outcomes of vaccinated children with their fully unvaccinated counterparts, as this would intentionally leave unvaccinated people and the communities they live in subject to increased risk of death and illness.

Should signals arise that there may be need for investigation, however, the report offers a framework for conducting safety research using existing or new data collection systems. One of the systems that the IOM report considered best suited to conduct these types of studies is CDC's Vaccine Safety Datalink (VSD). In response to the IOM report, CDC commissioned a white paper on the feasibility of conducting studies of the safety of the vaccine schedule in VSD. This report states, "Additionally, CDC has started conducting some of the studies mentioned in the white paper." Additional information on the white paper can be found at: https://www.cdc.gov/vaccinesafety/pdf/whitepapersafety_web.pdf.

(11) Please advise if you will:

a. prohibit conflict waivers for members of HHS's vaccine committees (ACIP, VRBPAC, NVAC & ACCV)?

HHS employs a thorough process for soliciting and vetting candidates for advisory committees to minimize any potential for financial conflicts of interest and works to identify all potential financial conflicts related to the particular matter before a committee. In accordance with 18 U.S.C. § 208(b)(1) and (b)(3), a member of an HHS vaccine advisory committee may be granted a waiver to allow individuals with potentially conflicting financial interests to participate in meetings where it concludes, after close scrutiny, that certain criteria are met. See 18 U.S.C. § 208 for more information.

b. prohibit HHS vaccine committee members or HHS employees with duties involving vaccines from accepting any compensation from a vaccine maker for five years?

The current federal ethics laws and regulations do not provide HHS or any other federal agency the authority to restrict the future employment of a career federal employee or an advisory committee member after they leave federal service. However, there are some restrictions on communication by former employees back to their federal agency, such as

a lifetime ban on communicating or appearing before the government on behalf of their new employer or anyone else regarding specific policy matters in which they participated personally and substantially during their entire government service. See 18 U.S.C § 207(a)(1) for more information. There are a number of other exceptions that may apply as well including restrictions on representations to the government for matters under the former employee's official responsibility and restrictions that apply to senior-level government officials.

Federal advisory committee members and career federal employees are prohibited from participating personally and substantially in a particular government matter that will affect their financial interests, as well as the financial interests of their spouse or minor child, general partner, or groups or people covered by 18 U.S.C. § 208. Many federal employees, depending on their duties, must file financial disclosure reports to help identify and mitigate potential conflicts of interest with the employees' duties. See 5 CFR Part 2634. Additionally, special government employees serving on advisory committees must report certain financial interests before attending committee meetings. *See* 5 CFR § 2634.904(a)(2). A 208(b)(3) waiver may be granted to such committee members, based on a determination that the need for the service outweighs the potential for a conflict of interest.

c. require that vaccine safety advocates comprise half of HHS's vaccine committees?

The Vaccine Act defines memberships for the NVAC and ACCV. See 42 U.S.C. §§ 300aa-5 and 300aa-19. The VRBPAC charter states that "Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of immunology, molecular biology, rDNA, virology; bacteriology, epidemiology or biostatistics, vaccine policy, vaccine safety science, federal immunization activities, vaccine development including translational and clinical evaluation programs, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry." You can learn more about the VRBAC charter at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129571.htm. The ACIP charter provides that "the committee shall consist of 15 members, including the Chair. Members and the Chair shall be selected by the Secretary, HHS, from authorities who are knowledgeable in the fields of immunization practices and public health, have expertise in the use of vaccines and other immunobiologic agents in clinical practice or preventive medicine, have expertise with clinical or laboratory vaccine research, or have expertise in assessment of vaccine efficacy and safety. The committee shall include a person or persons knowledgeable about consumer perspectives and/or social and community aspects of immunization programs." You can find out more about the ACIP by reading the charter at

https://www.cdc.gov/vaccines/acip/committee/charter.html. New members are selected based on the candidate's qualifications and their ability to contribute to the specific objectives or needs of the committee, with an overall goal of ensuring a diverse committee that reflects the charge.

d. allocate toward vaccine safety an amount at least equal to 50% of HHS's budget for promoting/purchasing vaccines?

The United States has a robust vaccine safety system that closely and constantly monitors the safety of vaccines. Several agencies within HHS dedicate a significant portion of their budgets and expertise to collaboratively ensure that vaccination efforts are as safe as possible. Due to the significant progress made in the last few years to monitor side effects and conduct relevant vaccine safety research, HHS does not foresee drastically changing current budget allocations in this area. However, this could change pending a vaccine safety signal. Likewise, advances in the development of new vaccines or ways of administering immunizations may require additional vaccine safety funding.

To address comments you made in your letter about vaccine monitoring, I want to clarify a few things. The Vaccine Adverse Event Reporting System (VAERS) is a national system to collect reports of adverse events that happen after vaccination. The adverse events reported to this system are not necessarily caused by vaccination and may or may not be a condition that occurred by chance alone, so they must be further investigated. For more information, please visit: https://vaers.hhs.gov/.

HHS places a priority on vaccine safety. To fulfill public health and regulatory functions, the Centers for Disease Control and Prevention (CDC) and FDA use the Vaccine Safety Datalink (VSD) and Post-licensure Rapid Immunization Safety Monitoring System (PRISM) to evaluate if adverse events are related to vaccination. You can find more details about VSD and PRISM at:
https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html and
http://onlinelibrary.wiley.com/doi/10.1002/pds.2323/abstract.

e. support the creation of a vaccine safety department independent of HHS?

HHS works in close partnership with other federal, state and local agencies, as well as private entities to monitor and communicate about the safety of U.S. vaccines. To adequately address safety-related issues, strengthen the system that monitors the safety of vaccines throughout production and use, and advance the safety profile of vaccines, the expertise of several groups within HHS is required. For example, FDA regulates vaccine clinical trials, licenses vaccines, and monitors vaccine safety after vaccine use and the Health Resources and Services Administration runs the National Vaccine Injury Compensation Program and the Countermeasures Injury Compensation Program. As HHS plays a significant and cross-cutting role in vaccine safety, the diverse federal

vaccine safety portfolio is coordinated at HHS to leverage collaboration among the many groups, inside and outside of HHS, involved in vaccine and immunization activities.

To address your point about conducting research to uncover long-term adverse events, HHS both conducts research in this area and funds outside research in this area. For example, after a safety signal in Europe indicated an increased risk of narcolepsy, a chronic neurological disorder caused by the brain's inability to normally regulate sleep-wake cycles, after vaccination with a monovalent 2009 H1N1 influenza vaccine, CDC began research to determine if there was a safety issue not only in the United States but globally as well. To respond to this signal, an international team of researchers conducted a dynamic retrospective cohort study to estimate incidence rates of narcolepsy diagnoses using a common protocol on electronic data in seven countries during 2003–2013. For the case control study, conducted according to a common protocol in six countries, cases were identified from sleep center records. Overall, the results of this study did not support an association between receipt of the 2009 H1N1 vaccine and narcolepsy. The successful completion of this study proves that the United States has the infrastructure to not only investigate vaccine safety signals at a local level, but to also collaborate with international partners when such signal is of global concern.

f. support the repeal of the 1986 Act to the extent it grants immunity to pharmaceutical companies for injuries caused by their vaccine products?
The National Vaccine Injury Compensation Program (VICP) does vital work to ensure an adequate supply of vaccines, stabilize vaccine costs, and establish and maintain an accessible and efficient forum for individuals found to be injured by certain vaccines. According to the VICP website, over 5000 petitions were compensated, supply shortages of vaccines have been reduced, and pricing of vaccines stabilized since the program was enacted. Likewise, this program provides an alternative to civil litigation that includes attorney fees and costs. Although the Vaccine Act provides liability protections to manufacturers of covered vaccines in many circumstances, these protections are not absolute. The Vaccine Act provides that there are instances when a manufacturer of a covered vaccine is not protected from liability by the Act, such as when an individual files a petition and is requesting damages of $1,000 or less. In such a case, a civil suit against an administrator may be permitted to be filed in state or Federal court without first filing a petition in the VICP.

Further, a repeal of the National Childhood Vaccine Injury Act of 1986 is unlikely. Congress recently passed the 21st Century Cures Act (Public Law 114-255), which made several amendments to the Vaccine Act. The amendments expand the VICP's coverage to include new vaccines that previously were not covered by the VICP (vaccines recommended by the CDC for routine administration in pregnant women) and make clear

that vaccine-injury claims may be filed both with respect to injuries alleged to have been sustained by women receiving covered vaccines during pregnancy and with respect to injuries alleged to have been sustained by live-born children who were in utero at the time those women were administered such vaccines.

Footnote 19

ICAN
Informed Consent Action Network

December 31, 2018

U.S. Department of Health & Human Services
HHS Office of the Secretary
Alex M. Azar II, Secretary of Health & Human Services
Tammy R. Beckham, Acting Director, National Vaccine Program Office
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *HHS Vaccine Safety Responsibilities and Notice Pursuant to 42 U.S.C. § 300aa-31*

Dear Secretary Azar and Acting Director Beckham:

In our letter of October 12, 2017, we notified HHS of a number of serious concerns regarding how the Department of Health & Human Services (**HHS**) fulfills its obligations to ensure vaccine safety under the National Childhood Vaccine Injury Act of 1986 (the **1986 Act**).[1] We voiced these concerns along with 55 other organizations who were copied on our letter and who represent over 5 million Americans.[2]

We thank HHS for the time and resources it dedicated to respond to our concerns in its letter of January 18, 2018, including having its response reviewed and cleared by the following agencies within HHS: the Centers for Disease Control and Prevention (**CDC**), Food & Drug Administration (**FDA**), National Institutes of Health (**NIH**), Office of the General Counsel (**OGC**), Human Resources & Services Administration (**HRSA**), and Agency for Healthcare Research and Quality (**AHRQ**).[3]

We write again because, after careful review, the substance of HHS's responses heightens the serious concerns we previously raised regarding the safety of HHS's childhood vaccine schedule.

As HHS is aware, the 1986 Act gave pharmaceutical companies immunity from liability for injuries caused by most of their vaccines and instead made vaccine safety the responsibility of HHS.[4] As the Secretary of HHS (the **Secretary**), you have the ultimate authority and responsibility to assure implementation of the vaccine safety obligations in

[1] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[2] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[3] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[4] 42 U.S.C. § 300aa-10; 42 U.S.C. § 300aa-11; 42 U.S.C. § 300aa-27; Bruesewitz v. Wyeth LLC, 562 U.S. 223 (2011)

the 1986 Act.[5] The importance of assuring the safety of the 71 vaccine doses injected into children pre-and-postnatally pursuant to HHS's vaccine schedule cannot be overstated.[6]

Given the gravity of HHS's responsibility, it is deeply troubling that the majority of HHS's letter contains little more than broad unsupported conclusory assertions. Most of these conclusory assertions do not withstand basic scrutiny. HHS's responses even often contradict its own source materials.

HHS's letter begins with the incorrect claim that the safety of many pediatric vaccines was investigated in clinical trials that included a placebo, and falsely implies these trials are typically longer than mere days or weeks. (Section I below). It then fails to support the safety of injecting babies with the Hepatitis B vaccine (Section II) and reaffirms HHS's refusal to: automate VAERS reporting (Section III); research the most commonly claimed vaccine-injury pairs (Section IV); identify which children will suffer a serious vaccine injury (Section V); pause claiming "Vaccines Do Not Cause Autism" until it has the studies to support this claim (Section VI); conduct vaccinated versus unvaccinated studies (Section VII); purge itself of conflicts of interest (Section VIII); or use the Vaccine Safety Datalink and PRISM to actually improve vaccine safety (Section IX).

History is replete with products that caused harm for years or decades longer than necessary because of gridlock at HHS.[7] The gridlock at HHS over vaccines makes that history look trivial.

A large and growing proportion of Americans have concerns regarding vaccines.[8] In order to persuade this population, including the over five million Americans represented by the groups listed on our opening letter, HHS must either substantiate that its vaccine schedule and representations regarding vaccine safety are based on rigorous and robust science, or acknowledge areas of failure to fulfill its vaccine safety duties. Unsupported and incorrect assertions will not suffice and will only deepen concerns regarding vaccine safety.

Only by providing the science to support vaccine safety or acknowledging shortcomings in this science can HHS begin to restore Americans' confidence in its ability to objectively assess and improve vaccine safety. Since parents and children are the most important stakeholders when it comes to vaccine safety, in addition to distributing these letters to the organizations listed in our opening letter, we intend to widely distribute these letters to the news media and the public at large.

---

[5] 42 U.S.C. § 300aa-27

[6] https://www.vaccines.gov/

[7] https://prescriptiondrugs.procon.org/view.resource.php?resourceID=005528

[8] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf ("an increasing number of parents have been expressing concerns about vaccine safety over the last two decades" and, in particular, "parents have been voicing concerns about the safety of the recommended immunization schedule as a whole"); https://www.hhs.gov/nvpo/featured-priorities/vaccine-confidence/index.html

I. INVALID PRE-LICENSURE SAFETY REVIEW OF PEDIATRIC VACCINES

In our opening letter, we asked that HHS identify the clinical trial data showing that the safety of pediatric vaccines was carefully studied *prior* to licensing and injecting them into millions of American children.[9] In response, HHS did not cite any such data. Instead, HHS merely made conclusory assertions regarding pediatric vaccine clinical trials that contradict HHS's published documents. We take each point in HHS's letter regarding vaccine clinical trials in turn below.

A. Placebo Controls Were Not Used in Pediatric Clinical Trials

Our opening letter expressed serious concern that the clinical trials relied upon to license pediatric vaccines did not include a control group receiving a placebo. Reflecting its importance, HHS's response letter addresses this concern in its first two sentences:

> I would like to address a comment made in Section II of your letter about pre-licensure safety review of pediatric vaccines. Contrary to statements made on page two of your letter, many pediatric vaccines have been investigated in clinical trials that included a placebo.[10]

Unfortunately, HHS's assertion that prior to licensure for children "many pediatric vaccines have been investigated in clinical trials that included a placebo" is untrue.

(i) HHS's False Claim Regarding Use of Placebos

As defined by the CDC, a "placebo" is: "A substance or treatment that has no effect on human beings."[11] As HHS is aware, common examples of a placebo are a saline injection or sugar pill.[12] The reason that drugs are first evaluated in a clinical trial against a placebo control group, prior to being released to the public, is to assess the drug's safety and effectiveness. As explained by HHS:

> In undertaking a clinical trial, researchers don't want to leave anything to chance. They want to be as certain as possible that the results of the testing show whether or not a treatment is safe and effective. The "gold standard" for testing interventions in people is the "randomized, placebo-controlled" clinical trial. ...

[9] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[10] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[11] https://www.cdc.gov/vaccines/terms/glossary.html
[12] https://www.ncbi.nlm.nih.gov/pubmed/1330942 ("a placebo is a pharmacologically inactive substance")

> A placebo is an inactive substance that looks like the drug or treatment being tested.[13]

However, for each pediatric vaccine – except one – that HHS promotes for routine injection into children, **the clinical trials relied upon to assess its safety prior to licensing its use in children did *not* use a placebo-control group**.

The following three tables, compiled from HHS's own publications, list each pediatric vaccine that HHS's vaccine schedule provides be routinely injected into American children.[14] Each table addresses a different age range and answers whether the trials relied upon to license each vaccine for use in children included at least one clinical trial that assessed its safety against a placebo control group.

According to HHS's childhood vaccine schedule, babies receive three injections of each of the following vaccines between day one and 6 months of life:

HHS'S CHILDHOOD SCHEDULE: ONE DAY TO 6 MONTHS OF LIFE			
VACCINE TYPE	**TEST GROUP RECEIVED**	**CONTROL GROUP RECEIVED[15]**	**PLACEBO CONTROL?**
DTaP	**Infanrix** (GSK)[16]	DTP	**NO**
	Daptacel (Sanofi)[17]	DT or DTP	**NO**
Hib	**ActHIB** (Sanofi)[18]	Hepatitis B Vaccine	**NO**
	Hiberix (GSK)[19]	ActHIB	**NO**
	PedvaxHIB (Merck)[20]	Lyophilized PedvaxHIB[21]	**NO**
Hepatitis B	**Engerix-B** (GSK)[22]	No control group	**NO**
	Recombivax HB (Merck)[23]	No control group	**NO**
Pneumococcal	**Prevnar 13** (Pfizer)[24]	Prevnar[25]	**NO**
Polio	**Ipol** (Sanofi)[26]	No control group	**NO**

[13] https://www.nia.nih.gov/health/why-are-placebos-important

[14] Pursuant to 21 C.F.R. 201.57 and other relevant regulations, the package insert for each vaccine is required to describe its "clinical trial experience," including identifying the "drug and comparators (e.g., placebo)," as well as accurately describe the clinical trials for each vaccine in its summary basis of approval and clinical trial review, and this letter assumes these documents, available on the FDA website, comply with these regulations. https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm

[15] Most vaccines had multiple trials; and where some trials used a control and others did not, only the control is listed.

[16] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm124514.pdf

[17] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm103037.pdf (lists DT vaccine in one of its efficacy trials as a "placebo")

[18] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109841.pdf

[19] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM179530.pdf

[20] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM253652.pdf

[21] In Lyophilized PedvaxHIB's pre-licensure trials, the test group received Lyphilized PedvaxHIB, OPV and DTP, and the control group received a placebo, OPV and DTP. Ibid. Concomitantly injecting OPV and DTP negate the benefit of having a placebo as it prevents assessing the actual safety profile between Lyophilized PedvaxHIB and a placebo.

[22] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf

[23] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf

[24] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM574852.pdf (While a placebo was used in trials for adults over 65 years old, no placebo was used in trials to license this vaccine for children.)

[25] "Prevnar" was also licensed without a placebo-controlled trial. http://labeling.pfizer.com/showlabeling.aspx?id=134

[26] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM133479.pdf

HHS'S CHILDHOOD SCHEDULE: ONE DAY TO 6 MONTHS OF LIFE			
VACCINE TYPE	**TEST GROUP RECEIVED**	**CONTROL GROUP RECEIVED[15]**	**PLACEBO CONTROL?**
Combination Vaccines	**Pediarix** (GSK)[27]	ActHIB, Engerix-B, Infanrix, IPV, and OPV	**NO**
	Pentacel (Sanofi)[28]	HCPDT, PolioVAX, ActHIB, Daptacel, and IPOL	**NO**

As the above table and HHS's own documentation show, there is not a single vaccine brand routinely injected into American children between day one and 6 months of life that was licensed based on a clinical trial which included a placebo-control group.

According to HHS's childhood vaccine schedule, babies receive a fourth injection of most vaccines in the table above as well as one or two injections of each of the following additional vaccines between 6 months and 18 months of life:

HHS'S CHILDHOOD SCHEDULE: 6 TO 18 MONTHS OF LIFE			
VACCINE TYPE	**TEST GROUP RECEIVED**	**CONTROL GROUP RECEIVED**	**PLACEBO CONTROL?**
Hepatitis A	**Havrix** (GSK)[29]	Engerix-B	**NO**
	Vaqta (Merck)[30]	AAHS and Thimerosal	**NO**
MMR	**M-M-R II** (Merck)[31]	No control group	**NO**
Chicken Pox	**Varicella** (Merck)[32]	Stabilizer and 45mg of Neomycin	**NO**
Combo Vaccine	**ProQuad** (Merck)[33]	M-M-R II and Varivax	**NO**
Flu[34]	**Fluarix (IIV4)** (GSK)[35]	Prevnar13, Havrix and/or Varivax or unlicensed vaccine	**NO**
	FluLaval (IIV4) (ID Bio)[36]	Fluzone (IIV4), Fluarix (IIV3) or Havrix	**NO**
	Fluzone (IIV4) (Sanofi)[37]	Fluzone (IIV3)	**NO**

[27] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM241874.pdf

[28] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109810.pdf (lists DT vaccine in one of its efficacy trials as a "placebo")

[29] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224555.pdf

[30] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110049.pdf ("Placebo (Alum Diluent)" contained 300µg AAHS and thimerosal, see https://www.nejm.org/doi/full/10.1056/NEJM199208133270702)

[31] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123789.pdf (The package insert for M-M-R-II cites a number of pre-licensure trials, typically with small sample sizes and often using children from orphanages, psychiatric institutions, or schools for the handicapped. In total, it cites: one trial for the M-M-R-II comparing it with other vaccines (ref. # 16), one for the measles vaccine in which the test and control group both received the measles vaccine (ref. # 7), three trials for the mumps vaccine in which controls were injected with various experimental vaccines (ref. # 8, 9, 11) and fifteen trials for the rubella vaccine comparing different types of rubella vaccine except for one trial with 23 apparently untreated controls and one trial with 19 controls receiving a saline nasal spray where rubella vaccine was also given intranasally (ref. # 1, 2, 19-26, 28, 29, 31, 56, 57).)

[32] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142813.pdf (While this insert states 465 children received a "placebo," Merck's peer reviewed publication explains the "placebo consisted of lyophilized stabilizer containing approximately 45 mg of neomycin." https://www.ncbi.nlm.nih.gov/pubmed/6325909. Neomycin is an antibiotic with serious side effects when swallowed, let alone injected: www.pdr.net/drug-summary/neomycin-sulfate?druglabelid=819&mode=preview)

[33] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123793.pdf (In one clinical trial, 799 children received ProQuad+Placebo, MMR II+Placebo, or MMR II+Varivax, but none received only a placebo; hence, this was not a placebo-controlled trial nor does it pretend to be in its Clinical Review: http://wayback.archive-it.org/7993/20170723150913/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123800.pdf)

[34] This and the next table include all flu shots the CDC lists for injection into children for the 2018-2019 flu season. https://www.cdc.gov/flu/protect/vaccine/vaccines.htm. One flu vaccine, FluMist (LAIV4), is given via nasal spray, not injection, and hence not discussed.

[35] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619534.pdf (placebo control only used in adult trials but unfortunately never in trials to license this vaccine for children)

[36] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619548.pdf

[37] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM356094.pdf

As the above table and HHS's own documentation show, there is not a single vaccine brand routinely injected into American babies between 6 months and 18 months of life that was licensed based on a clinical trial which included a placebo-control group.

Finally, according to HHS's childhood vaccine schedule, children receive yet another injection of a majority of the vaccines in the above two tables as well as one to three injections of each of the following additional vaccines, along with an annual influenza vaccine, between 18 months and 18 years of life:

HHS'S CHILDHOOD SCHEDULE: 18 MONTHS TO 18 YEARS OF LIFE			
VACCINE TYPE	**TEST GROUP RECEIVED**	**CONTROL GROUP RECEIVED**	**PLACEBO CONTROL?**
Tdap	**Boostrix** (GSK)[38]	DECAVAC or Adacel	**NO**
	Adacel (Sanofi)[39]	Td (for adult use)	**NO**
HPV	**Gardasil** (Merck)[40]	AAHS *or* Gardasil carrier solution (Sodium Chloride, L-histidine, Polysorbate 80, Sodium Chloride, and Yeast Protein) (594 subjects)	**NO**
	Gardasil-9 (Merck)[41]	Gardasil *or* Placebo (306 subjects that recently received 3 doses of Gardasil)	**YES**[42]
Mening-ococcal	**Menactra** (Sanofi)[43]	Menomune	**NO**
	Menveo (GSK)[44]	Menomune, Boostrix, Menactra, or Mencevax	**NO**
Combination Vaccines	**Kinrix** (GSK)[45]	Infanrix and Ipol	**NO**
	Quadracel (Sanofi)[46]	Daptacel and Ipol	**NO**
Flu[47]	**Afluria (IIV3)** (Seqirus)[48]	Fluzone (IIV3)	**NO**
	Afluria (IIV4) (Seqirus)[49]	Fluarix (IIV4)	**NO**
	Flucelvax (IIV4) (Seqirus)[50]	Flucelvax (IIV3) or a (Seqirus) investigational vaccine	**NO**

[38] https://www.fda.gov/downloads/BiologicsBloodVaccines/UCM152842.pdf

[39] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142764.pdf

[40] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf (While this insert states 594 controls received a "saline placebo," Merck's peer reviewed publication explains the "placebo used in this study contained identical components to those in the vaccine, with the exception of HPV L1 VLPs and aluminum adjuvant," which means this "placebo" contained Sodium Chloride, L-histidine, Polysorbate 80, Sodium Chloride, and Yeast Protein. https://www.ncbi.nlm.nih.gov/pubmed/17484215)

[41] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM429166.pdf

[42] In only one clinical trial, 306 controls received a placebo, and Merck required the 618 subjects in this trial receiving Gardasil-9 to have recently received 3 doses of Gardasil and be in good health. https://clinicaltrials.gov/ct2/show/NCT01047345. Generalized safety conclusions therefore cannot be made from this small trial since it only included subjects with a proven record of receiving Gardasil without health complications. This trial does, however, prove that a saline placebo can be used in vaccine clinical trials.

[43] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM131170.pdf (In one clinical trial, 509 adolescents (between 11 and 18 years of age) received Td for Adult Use plus Menactra and 28 days later received a saline injection, and 512 adolescence received Td for Adult Use plus a saline injection and 28 days later received Menactra. Despite including a saline injection, this is not a placebo-controlled trial nor does it pretend to be in its Clinical Review: http://wayback.archive-it.org/7993/20170722073019/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm176044.htm)

[44] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201349.pdf

[45] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM241453.pdf

[46] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM439903.pdf

[47] This and the prior table list all injectable flu shots for children for the current flu season: https://www.cdc.gov/flu/protect/vaccine/vaccines.htm

[48] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM263239.pdf (placebo control only used in adult trials but unfortunately never in trials to license this vaccine for children)

[49] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM518295.pdf

[50] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619588.pdf (placebo control only used in adult trials but unfortunately never in trials to license this vaccine for children)

As the above three tables and HHS's own documentation establish, only one out of 30 vaccines brands routinely injected into American children was licensed based on a clinical trial which had a placebo-control group.[51]

The use of placebo control groups is essential to protect society from the harm that could result from widespread use of ineffective or unsafe medical treatments. The fact that HHS does not and apparently will not require pharmaceutical companies to use a placebo control in pediatric vaccine clinical trials evidences HHS's lack of confidence in the safety profile of these products. If HHS had confidence in their safety profiles, it would require that vaccine clinical trials – as is typical for drug clinical trials – include a placebo-control group. For example, drugs such as Botox,[52] Prozac,[53] and Lipitor,[54] typically given to adults rather than children, have placebo controls in their clinical trials. Like almost all drugs, pediatric vaccines should be licensed based on placebo-controlled clinical trials so that HHS can assess their safety profiles prior to approving them for injection into millions of children.

It is troubling that HHS chose to begin its response by misstating that prior to licensure for children "many pediatric vaccines have been investigated in clinical trials that included a placebo."[55] At worst, HHS knowingly perpetuated this inaccurate claim, but at best, HHS was unaware this claim was incorrect. This leaves the public to wonder what other critical assumptions underpinning HHS's confidence in vaccine safety are incorrect.

(ii) HHS Licenses New Vaccines Without Any Placebo-Controlled Trial Even When No Vaccine for the Same Disease Exists

After making the false claim that many vaccines on HHS's childhood schedule were licensed based on a placebo-controlled trial, HHS then states:

> Inert placebo controls are not required to understand the safety profile of a new vaccine, and are thus not required.

This claim is astonishing. For almost all new drugs, especially where no substantially similar product is already licensed, HHS's guidance expects a placebo control group to be part of the clinical trial so that the adverse event rate in the test group receiving the new drug can be assessed against the rate in the placebo group.

---

[51] Both Rotavirus vaccines are given via oral drop and hence not discussed. Nonetheless, RotaTeq (Merck)'s "placebo" contained Polysorbate 80, Sucrose, Citrate and Phosphate, and Rotarix (GSK)'s "placebo" contained Sucrose, Dextran, Sorbitol, Amino acids, Dulbecco's Modified Eagle Medium, Calcium Carbonate, and Xanthan. https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM133539.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142288.pdf

[52] https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5236lbl.pdf

[53] https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018936s091lbl.pdf

[54] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf

[55] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

HHS's industry guidance explains that using another drug as a so-called "active control" is only appropriate if it is for a similar indication and is a "drug whose effect is well-defined," which means "historical placebo-controlled trials are available to define the active control effect."[56] As the FDA explains:

> The placebo-controlled trial measures the total pharmacologically mediated effect of treatment. In contrast, an active control trial … measures the effect relative to another treatment. The placebo-controlled trial also allows a distinction between adverse events due to the drug and those due to the underlying disease or background noise.[57]

Hence, the reason researchers do not use a non-inert substance as a control is because, due to its pharmacological effects, it makes it impossible to isolate the effects of just the experimental product being studied. Nevertheless, a placebo control was only used in only one tiny clinical trial for one of the 30 vaccine brands listed in the tables above.

The critical difference between using an inert and non-inert substance as a control can be clearly seen from the trials relied upon to license Gardasil in 2006. The manufacturer's package insert for Gardasil states that it was licensed based on a clinical trial in which: (i) 10,706 women received Gardasil; (ii) 9,092 women received 225 mcg or 450 mcg of Amorphous Aluminum Hydroxyphosphate Sulfate (**AAHS**) – the so-called "AAHS Control" (aluminum adjuvant, such as AAHS, is a known cytotoxic and neurotoxic substance used to induce autoimmunity in lab animals, and which numerous peer-reviewed publications implicate in various autoimmune conditions[58]); and (iii) 320 women received a "Saline Placebo."[59] During the six month study follow-up, 2.3% of the women receiving Gardasil (the "test group") and 2.3% of the women receiving the AAHS Control or Saline Placebo (the "combined control group") reported developing a systemic autoimmune disorder.[60] Since the rate of systemic autoimmune disorders in the "test group" and the "combined control group" were similar, the vaccine was deemed safe and licensed by HHS.

---

[56] https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf

[57] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073139.pdf. Also see https://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm ("There are three principal difficulties in interpreting active-control trials. … One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have powerful stimuli toward assuring study excellence. *Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds of poor study quality that can arise.* The other problem is that a finding of no difference between a test article and an effective treatment may not be meaningful.")

[58] https://www.wiley.com/en-us/Vaccines+and+Autoimmunity-p-9781118663431; https://www.ncbi.nlm.nih.gov/pubmed/25923134

[59] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf

[60] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf

What the manufacturer's package insert for Gardasil given to the public failed to disclose is that the Saline Placebo group had *zero* cases of systemic autoimmune disorder (when 7 cases – 2.3% of 320 subjects – would be expected if autoimmune disorders were equally distributed among the Saline Placebo and AAHS Control recipients).[61] This fact was obfuscated by combining the small Saline Placebo group with the large AAHS Control group into a single control group and reporting their combined systemic autoimmune disorder rate, even though all the cases of autoimmunity came from the AAHS Control group.[62] The following is an excerpt from Gardasil's package insert with the combined control group highlighted in yellow:

Table 9: Summary of Girls and Women 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality

Conditions	GARDASIL (N = 10,706)	AAHS Control* or Saline Placebo (N = 9412)
	n (%)	n (%)
Arthralgia/Arthritis/Arthropathy†	120 (1.1)	98 (1.0)
Autoimmune Thyroiditis	4 (0.0)	1 (0.0)
Celiac Disease	10 (0.1)	6 (0.1)
Diabetes Mellitus Insulin-dependent	2 (0.0)	2 (0.0)
Erythema Nodosum	2 (0.0)	4 (0.0)
Hyperthyroidism	27 (0.3)	21 (0.2)
Hypothyroidism	35 (0.3)	38 (0.4)
Infalmmatory Bowel Disease	7 (0.1)	10 (0.1)
Multiple Sclerosis	2 (0.0)	4 (0.0)
Nephritis	2 (0.0)	5 (0.1)
Optic Neuritis	2 (0.0)	0 (0.0)
Pigmentation Disorder	4 (0.0)	3 (0.0)
Psoriasis	13 (0.1)	15 (0.2)
Raynaud's Phenomenon	3 (0.0)	4 (0.0)
Rheumatoid Arthritis	6 (0.1)	2 (0.0)
Scleroderma/Morphea	2 (0.0)	1 (0.0)
Stevens-Johnson Syndrome	1 (0.0)	0 (0.0)
Systemic Lupus Erythematosus	1 (0.0)	3 (0.0)
Uveitis	3 (0.0)	1 (0.0)
All Conditions	245 (2.3)	218 (2.3)

†AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

The fact that the Saline Placebo group had no cases of systemic autoimmune disorder is what would be expected.[63] It is not normal for 2.3% of previously healthy girls and women to develop a systemic autoimmune disorder within six months of the commencement of a clinical trial unless there was some environmental exposure that caused the harm, such as an injection of Gardasil or AAHS. This finding is nonetheless ignored because, to license this vaccine, HHS permitted AAHS to serve as the control.

It was also unethical to inject almost 10,000 girls and women with a known neurotoxin like AAHS, which has no therapeutic benefit.[64] The transparent purpose of this unethical study design was to create a "control group" that would yield a similar adverse event rate to the "test group" receiving Gardasil. In this manner the trial masked a serious

[61] https://www.clinicaltrials.gov/ct2/show/results/NCT00092547?term=nct+00092547&rank=1&sect=X430156&view=results
[62] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf
[63] https://www.clinicaltrials.gov/ct2/show/results/NCT00092547?term=nct+00092547&rank=1&sect=X430156&view=results
[64] https://www.wiley.com/en-us/Vaccines+and+Autoimmunity-p-9781118663431

safety issue with Gardasil that should have prevented its licensure.[65] Furthermore, there was no excuse for not requiring a placebo control (saline injection) in clinical trials for Gardasil because, at that time, no other vaccine was yet licensed for the four HPV strains Gardasil was intended to prevent.

As the Gardasil clinical trial shows, HHS does not require a placebo control group for clinical trials of even an entirely new vaccine for an infection for which no other vaccine exists. Another example is the Hepatitis A vaccine.

There are only two Hepatitis A vaccines on the market: Havrix (GSK), licensed in 1995, and Vaqta (Merck), licensed in 1996.[66] Because the clinical trials for both were conducted when there was no Hepatitis A vaccine on the market, these trials should certainly have used a placebo control to assess their safety. Yet, the safety profile for these products was never assessed using a placebo control. Instead, the trial for Havrix had no control group and the trial for Vaqta used AAHS and Thimerosal as a control.[67] The lack of a placebo control in the clinical trials relied upon to license Havrix was such a clear lapse in safety for an entirely new vaccine (for an infection that had no previously licensed vaccine) that its Clinical Review even made a point to disclaim: "There were no placebo controls."[68]

A third example is Varivax (Merck), the very first vaccine licensed for varicella (chicken pox). Varivax was also licensed without any placebo-controlled clinical trial. Recognizing the importance of a placebo control, the package insert for Varivax claims that its safety was reviewed against a "placebo" control.[69] Putting aside that only 465 children received the purported "placebo," Merck's peer reviewed article regarding this trial makes clear this "placebo" was not a placebo, but rather an injection of "lyophilized stabilizer containing approximately 45 mg of neomycin per milliliter."[70] Neomycin is an antibiotic which, in oral form, has a long list of serious adverse reactions, such as hearing loss, kidney problems and nerve problems.[71] An injection which includes neomycin is therefore plainly *not* a placebo. Using a control that can have serious adverse reactions when orally ingested, let alone injected, obfuscated Varivax's actual safety profile.[72]

It is unethical and unacceptable that a placebo control, such as a saline injection, was not used for entirely new vaccines, such as for Hepatitis A and Varicella. Even worse, as

---

[65] This defective clinical trial design may have been influenced by the HHS agency and its employees that developed the patent used to develop Gardasil and receive royalties from its sale. https://www.ott.nih.gov/news/nih-technology-licensed-merck-hpv-vaccine

[66] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/us-vaccines.pdf

[67] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110049.pdf (The "Placebo (Alum Diluent)" contained 300µg AAHS and thimerosal, https://www.nejm.org/doi/full/10.1056/NEJM199208133270702)

[68] http://wayback.archive-it.org/7993/20170723025039/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110035.pdf

[69] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142813.pdf

[70] Ibid.; https://www.ncbi.nlm.nih.gov/pubmed/6325909

[71] www.pdr.net/drug-summary/neomycin-sulfate?druglabelid=819&mode=preview

[72] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142812.pdf

the next section shows, these same vaccines are then used as an "active control" for licensing other vaccines despite having never been safety tested for licensure themselves in a placebo-controlled trial. The use of medications and vaccines in the practice of medicine is ethically justified if the benefits substantially outweigh the harms.[73] When studies to approve vaccines are conducted in which the harms are not accurately assessed because there is no placebo control group, then the use of those vaccines is not justified.[74]

(iii) HHS's "Safety" Pyramid Scheme

After licensing a vaccine without assessing its safety in a placebo-controlled clinical trial, HHS will then often license another vaccine as long as it has a similar adverse event rate to the licensed (but improperly safety tested) vaccine. This is a so-called "active control," which HHS references in its letter. But this form of comparison only provides reliable safety data if the previously licensed "active control" itself had its safety profile previously assessed in a properly designed placebo-controlled trial.

HHS's own industry guidance for drug testing explains that an active control is only appropriate if it is a "drug whose effect is well-defined," which means "historical placebo-controlled trials are available to define the active control effect."[75] Despite its own policy and guidance, HHS does not require this minimal assurance for vaccines. Instead, all vaccines on HHS's pediatric schedule were licensed based on a clinical trial with no control whatsoever, or another vaccine/substance used as a control which itself was never licensed based on a placebo-controlled trial. As noted in our opening letter:

> [Pediatric vaccines] either had no control group or a control group which received other vaccines as a "placebo." This means each new vaccine need only be roughly as safe as one (or in some cases numerous) previously licensed vaccines. Such flawed and unscientific study designs cannot establish the actual safety profile of any vaccine. The real adverse event rate for a vaccine can only be determined by comparing subjects receiving the vaccine with those receiving an inert placebo. Yet, this basic study design, required for every drug, is not required before or after licensing a vaccine.[76]

Nonetheless, HHS claims in its letter that when an active control is used "the adverse event profile of that control group is usually known."[77] But this claim is incorrect for all "active

[73] https://global.oup.com/ushe/product/principles-of-biomedical-ethics-9780199924585?cc=us&lang=en&
[74] https://www.ncbi.nlm.nih.gov/pubmed/4907496
[75] https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf
[76] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[77] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

controls" used to license any vaccine on HHS's childhood vaccine schedule because none of these "active controls" were licensed based on a placebo-controlled trial.

Prevnar 13 provides a good first example of how HHS's claim is incorrect. HHS recommends that every child receive this vaccine at 2, 4, 6, and 12 months of age.[78] HHS licensed this vaccine in 2010 without a clinical trial assessing its safety in children against a placebo control.[79] Instead, it permitted a previously licensed vaccine, Prevnar, to act as the control.[80] However, like Prevnar 13, HHS licensed Prevnar without a clinical trial assessing its safety against a placebo control.[81] Rather, HHS licensed Prevnar based on a clinical trial in which the control was "an investigational meningococcal group C conjugate vaccine [MnCC]."[82] MnCC, in turn, an unlicensed product, was also never licensed based on any placebo-controlled trial.[83]

The clinical trial for Prevnar 13 found that "Serious adverse events reported following vaccination in infants and toddlers occurred in 8.2% among Prevnar 13 recipients and 7.2% among Prevnar recipients."[84] Despite this finding, Prevnar 13 was deemed safe and therefore licensed for use in babies because it had a similar serious adverse reaction rate as the control group receiving Prevnar.[85] But a comparison with Prevnar was an invalid measure of safety because Prevnar was safety tested prior to licensure against another experimental vaccine. As a group of FDA and CDC scientists conceded after Prevnar was licensed:

> Prior to licensure, … the control group in [Prevnar's] main study received another experimental vaccine, rather than a placebo. If both vaccines provoked similar adverse effects, little or no difference between the 2 groups might have been evident.[86]

Hence, the trial for Prevnar 13, in which both the Prevnar 13 and Prevnar groups have a 7% to 8% serious adverse event rate, could and should have caused serious concern regarding the safety of both vaccines. Instead, Prevnar 13 was deemed safe because it was as safe as Prevnar. But, as shown, Prevnar itself was only deemed safe because it was tested against an unlicensed experimental vaccine.

---

[78] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
[79] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf
[80] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf; http://labeling.pfizer.com/showlabeling.aspx?id=134
[81] http://labeling.pfizer.com/showlabeling.aspx?id=134
[82] http://labeling.pfizer.com/showlabeling.aspx?id=134
[83] See tables above.
[84] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf
[85] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf
[86] https://www.ncbi.nlm.nih.gov/pubmed/15479935

A second example is Heplisav-B, the most recent vaccine approved by HHS.[87] The trials for this new Hepatitis B vaccine, which contains a novel adjuvant, did not use a placebo control.[88] Instead, the control was Engerix-B.[89] The serious adverse event rate in the primary clinical trial for Heplisav-B was 6.2%, which the researchers deemed similar to the serious adverse event rate of 5.3% for Engerix-B.[90] Heplisav-B was therefore deemed safe only because it was as safe as Engerix-B, but Engerix-B was licensed based on a clinical trial without any control, let alone a placebo control.[91] As such, the serious adverse reaction rate for Engerix-B and Heplisav-B should have caused serious concern regarding the safety of both vaccines, not confidence that Heplisav-B is safe.

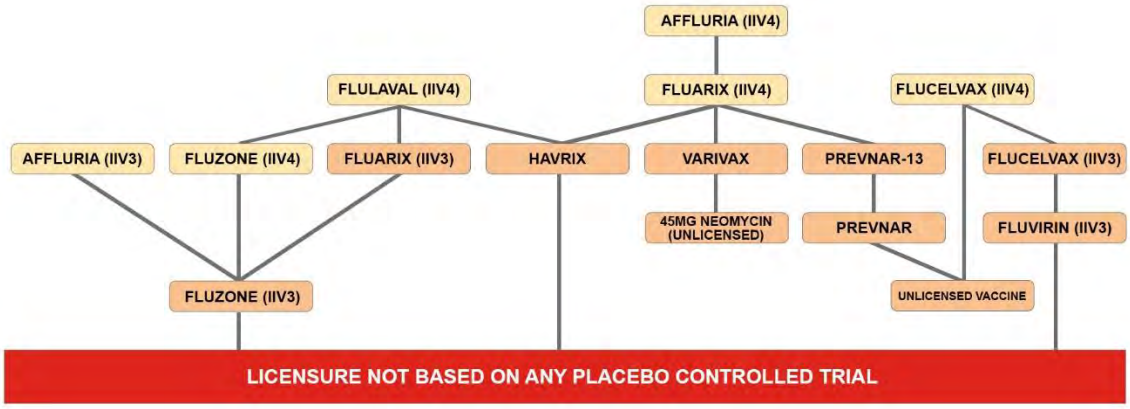
A third example are influenza vaccines (flu shots). In 1980, HHS licensed Fluzone (IIV3) without assessing its safety against a placebo control.[92] Nonetheless, Fluzone (IIV3) was used as the control in the trials relied upon to license Afluria (IIV3) in 2007 and Fluzone (IIV4) in 2013 for children.[93] Shortly thereafter, Fluzone (IIV4), Fluarix (IIV3) or Havrix were then used as the controls in the clinical trials supporting the licensure of FluLaval (IIV4).[94] This entire pyramid scheme rests on the safety of Fluzone (IIV3) which was licensed for pediatric use based on a trial without any control, let alone a placebo control.[95]

Similarly, Fluarix (IIV4) was licensed for children in 2012 based on a trial using Prevnar 13, Havrix and/or Varivax as controls; Fluarix (IIV4) was then used as the control to license Afluria (IIV4) in 2016.[96] This means Afluria (IIV4) was licensed because it was deemed as safe as Fluarix (IIV4), and that vaccine was licensed because it was deemed as safe as Prevnar 13, Havrix, or Varivax. However, the latter two were licensed without a placebo control; and Prevnar 13 was licensed because it was as safe as Prevnar, but that vaccine was only licensed because it was as safe as "an investigational meningococcal group C conjugate vaccine." Hence, at bottom, none of those vaccines had its safety profile established based on any placebo-controlled clinical trial. On this basis alone the ethics of recommending routine injection of these vaccines into children is questionable.

---

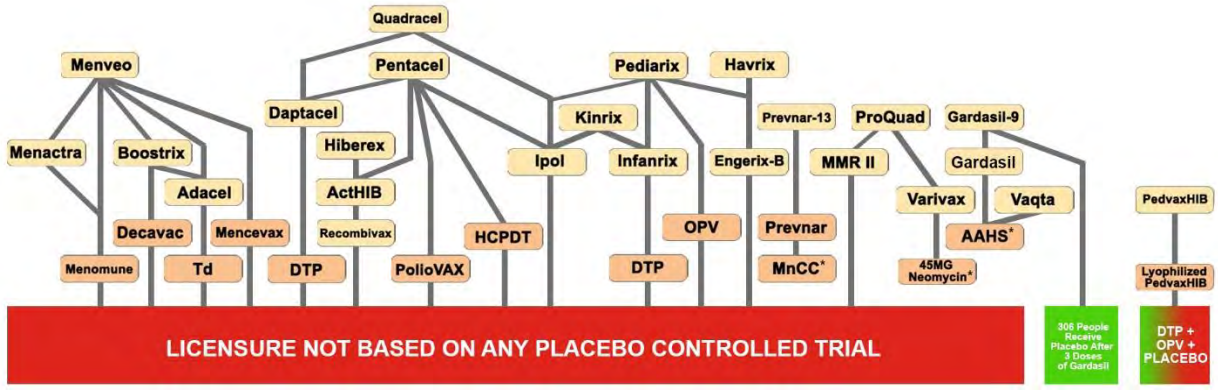
[87] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM584762.pdf
[88] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM584762.pdf
[89] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM584762.pdf
[90] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM584762.pdf
[91] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf
[92] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619664.pdf (Researchers did conduct one efficacy trial for Fluzone (IIV3) long *after* it was licensed which found that "the rate of hospitalization was actually higher in the vaccine group than in the placebo group" with 60% more vaccinated than unvaccinated children being hospitalized for insertion of ear draining tubes. https://www.ncbi.nlm.nih.gov/pubmed/14506120)
[93] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM263239.pdf (placebo control only used in adult trials but never in trials to license this vaccine for children); https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM356094.pdf
[94] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619548.pdf
[95] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619664.pdf
[96] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM220624.pdf (44% and 45% of the Fluarix (IIV4) and comparator vaccine group, respectively, reported an unsolicited adverse event within 28 days and 3.6% and 3.3%, respectively, reported a serious adverse reaction)

The following diagram highlights in yellow each flu shot recommended for injection into children during the 2018-2019 flu season; and each descending line shows the control(s) used to license the vaccine above[97]:



As the above diagram makes clear, HHS did not rely on a single placebo-controlled trial to license any flu shot HHS recommends for injection into every child over 6 months of age during the upcoming flu season.

The above examples demonstrate how HHS licenses vaccines by relying on a pyramid of other vaccines that were each licensed without being properly safety tested in a placebo-controlled trial. The diagram below highlights in yellow each vaccine HHS's childhood vaccine schedule lists for routine use (except for influenza vaccines already depicted in the diagram above), and each descending line shows the control(s) used to license the vaccine above:



*Unlicensed

As is clear, at the bottom of this pyramid there is not a single placebo-controlled trial relied upon to license any vaccine in this pyramid scheme (with the exception of Gardasil-9 in which 306 individuals received a saline injection after three shots of Gardasil).

[97] https://www.cdc.gov/flu/protect/vaccine/vaccines.htm

It is deeply troubling that HHS permits pharmaceutical companies to use "active controls" in clinical trials for new vaccines when none of the "control vaccines" were themselves licensed based on a placebo-controlled trial. This creates layers of assumptions regarding safety that resemble a pyramid scheme. Tracing back the pre-licensure clinical trial for each vaccine used as an active control, one finds that the initial vaccine in the "safety chain" was either licensed without any control group or assessed against another vaccine, including vaccines, such as DTP, which were withdrawn from use due to safety concerns.

(iv) HHS Summarily Dismisses Claims of Vaccine Harm

The lack of a placebo in clinical trials is even more troubling because, when parents assert that a vaccine injured their child, HHS regularly denies these assertions by stating that no cause and effect has been established between vaccination and the alleged injury. But as HHS is well aware, *without* a placebo control trial, cause and effect is very difficult and often impossible to establish.[98] Therefore, no matter how many or what type of vaccine injuries are reported, HHS and manufacturers can and do hide behind the claim that "a cause and effect relationship with the vaccine has not been established."[99]

This avoidance of proper research is reflected in the package insert for each pediatric vaccine. As required by federal law, each package insert lists the serious adverse events reported by doctors and consumers *after* licensure of the vaccine.[100] Federal law is also clear that this list should include "*only* those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."[101] Appendix B to this letter provides a partial (yet long) list of reported post-licensure reactions listed on pediatric vaccine package inserts, including numerous neurological, brain and immune system disorders.

Instead of these serious adverse event reports resulting in a call to action by HHS to finally conduct long-term studies that could reasonably establish if these adverse events are causally related to vaccination, the response has been the opposite. HHS continues with growing intransigence to hide behind the claim that no causation has been proven. HHS even requires that every vaccine package insert include the following disclaimer before the list of vaccine-related adverse events reported by doctors and consumers post-licensure:

---

[98] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html ("establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible," rather, researchers need "to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons"); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505292/ (The entire advantage of a randomized placebo-controlled trial "is the ability to demonstrate causality i.e., cause-effect relationship."); https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html (The Vaccine Adverse Events Reporting System (VAERS) is unable "to determine causation" because "there is a lack of an unvaccinated group for comparison in VAERS.")

[99] Ibid.

[100] 21 C.F.R. 201.57

[101] 21 C.F.R. 201.57

> In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for [vaccine brand] since market introduction of this vaccine are listed below. This list includes serious adverse events or events which have a suspected causal connection to components of [vaccine brand] or other vaccines or drugs. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.[102]

But without carrying out placebo controlled clinical trials, which can determine causation statistically, (and by ignoring existing experimental studies in animal models aimed at establishing the underlying biological mechanisms of potential vaccine injuries,) HHS can, and apparently will, continue to hide behind this disclaimer indefinitely.

As reflected in Appendix B, there is a consistent theme of autoimmunity and neurological disorders running across the serious post-licensure adverse events reported in vaccine package inserts. Yet, HHS refuses to require placebo-controlled clinical trials to determine if any of these events are actually caused by vaccination. HHS claims doing so would be unethical for clinical trials evaluating the safety of an experimental vaccine when there is already a vaccine licensed for the same disease because it would leave a child that could be vaccinated for that disease unvaccinated. This ethical concern however rings hollow, because if ethics were a real concern, HHS would require placebo-controlled trials before licensing each new experimental vaccine where no vaccine yet exists for the infection it is intended to prevent. For example, before licensing the first Hepatitis A or Varicella vaccines as discussed above.

Conducting a placebo-controlled clinical trial will leave a clearly defined group of children unvaccinated only during the duration of the trial in a controlled setting where they can be monitored.[103] In contrast, injecting a vaccine into millions of children in an uncontrolled setting without first having any placebo-controlled trial safety data is, to any objective reasonable observer, grossly unethical conduct.[104] In a comparable situation where the baseline of safety for the "active control" had not been established, researchers from the University of Oxford explained:

---

[102] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075057.pdf

[103] There are already hundreds of thousands of children that are completely unvaccinated in this country. https://www.cdc.gov/mmwr/volumes/67/wr/mm6740a4.htm For example, there are many parents that will not vaccinate due to religious beliefs.

[104] https://history.nih.gov/research/downloads/nuremberg.pdf ("voluntary consent ... means that the person … should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision")

> In some trials placebos were omitted on ethical grounds. This is illogical because studies destined to produce unreliable results should themselves be considered unethical.[105]

As a result, the only "ethical" thing to do at this point is for HHS to comprehensively and impartially fund truly neutral third-parties to conduct placebo-controlled trials for each vaccine and the entire HHS childhood vaccine schedule.

By refusing to conduct any placebo-controlled studies – even for new vaccines for diseases for which no vaccine exists yet – HHS provides itself a convenient way to consistently discount even widespread reported claims of vaccine injury by simply claiming causation has not been proven, knowing full well causation will likely never be proven – one way or another – without a placebo-controlled trial.[106]

The near universal failure to employ a placebo control group in pediatric vaccine clinical trials is scientifically and morally indefensible. The importance of a placebo control group is no doubt why HHS felt compelled to address that point first in its lengthy response letter. And now that HHS knows it was incorrect to claim that prior to licensure "many pediatric vaccines have been investigated in clinical trials that included a placebo," we expect that HHS will address this serious shortcoming by actually conducting appropriate placebo-controlled trials.

B. Duration of Safety Review

In our letter we also questioned the length of time vaccine trials gather and assess adverse reactions, noting as examples that the two Hepatitis B vaccines injected into infants assessed adverse reactions for only four[107] and five[108] days, respectively, and that the only stand-alone polio vaccine reviewed safety for a mere 48 hours.[109] In response, HHS's letter seeks to create the false impression that the safety review period for pediatric vaccine clinical trials occurs over an extended period of time, stating:

> In addition, there appears to be a misunderstanding regarding the term "solicited" adverse events. Typically, in vaccine trials,

---

[105] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1113953/

[106] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html ("establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible," rather, researchers need "to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons"); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505292/ (The entire advantage of a randomized placebo-controlled trial "is the ability to demonstrate causality i.e., cause-effect relationship."); https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html (The Vaccine Adverse Events Reporting System (VAERS) is unable "to determine causation" because "there is a lack of an unvaccinated group for comparison in VAERS.")

[107] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf

[108] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf

[109] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM133479.pdf

> the incidence of certain specific clinical findings that might be expected after vaccination is monitored for a short period of time after vaccination. Because these events are pre-specified, they are considered to be "solicited" events. In addition, other unexpected or severe adverse events, which may occur over a longer period of time following vaccination, are also analyzed and evaluated by FDA, but because these events are not predicted prior to initiation of the study, these are not called "solicited" adverse events.[110]

There was no misunderstanding regarding "solicited" versus "unsolicited" adverse events in our initial letter. The duration that solicited *or* unsolicited adverse events are tracked in pediatric vaccine clinical trials is typically far too short to detect adverse effects beyond a few days or weeks of vaccination. This is no doubt why HHS vaguely refers to "short period" versus "longer period" without actually specifying the duration of the so-called "longer period." As HHS knows, the "longer period" is still often only days or weeks, or at most a few months, instead of the several years needed to assess the actual safety profile after injecting a baby.

Whether reviewing solicited or unsolicited events, vaccine clinical trials are almost always far too short to capture developmental delays, autoimmune issues, and other chronic conditions that are likely to be diagnosed only years after vaccination.

(i) Safety Review Periods in Clinical Trials for Pediatric Vaccines are Too Short to Detect Most Chronic Health Conditions

HHS's own publications leave no doubt as to the incredibly short safety review period for almost all vaccines on HHS's childhood vaccine schedule.

On the *first day of life*, HHS's schedule instructs that all newborns receive a Hepatitis B vaccine.[111] The two Hepatitis B vaccines licensed in the United States for newborns are Recombivax HB (Merck) and Engerix-B (GSK).[112] Both were licensed based on clinical trials which reviewed so-called solicited and unsolicited reactions for no longer than *five days after vaccination*.[113] As required by HHS's own regulations[114], the clinical trial experience upon

[110] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[111] HHS purposely shifted the burden of this vaccine from those at risk, such as intravenous drug users, to all newborns. https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm
[112] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/us-vaccines.pdf
[113] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf
[114] 21 CFR 201.57(c)(7)

which the licensure of each vaccine is based must be summarized in its package insert, and the inserts for these two vaccines explain as follows:

> "In three clinical studies, 434 doses of RECOMBIVAX HB, 5 mcg, were administered to 147 healthy infants and children (up to 10 years of age) *who were monitored for 5 days after each dose*."[115]

> "In 36 clinical studies, a total of 13,495 doses of ENGERIX-B were administered to 5,071 healthy adults and children who were initially seronegative for hepatitis B markers, and healthy neonates. *All subjects were monitored for 4 days post-administration*."[116]

Putting aside that the number of babies in these trials is unclear, five days is not long enough to assess the safety profile of these products. Moreover, without a placebo control, these trials do not even provide an actual safety profile for the five days in which safety was purportedly reviewed.

At *two months of life*, HHS's schedule instructs that babies be injected with the Hepatitis B, Hib, DTaP, IPV, and PCV 13 vaccines.[117] The safety review period of so-called solicited and unsolicited adverse reactions in the trials relied upon to license these vaccines were also too short to capture any resulting chronic health conditions. This is confirmed by HHS's own documentation for each:

Target Disease	Product Name (Manufacturer)	Duration of Safety Review After Injection	
		Solicited Reactions	Unsolicited Reactions
Hepatitis B	Recombivax HB (Merck)[118]	5 days	5 days
	Engerix-B (GSK)[119]	4 days	4 days
Hib	ActHIB (Sanofi)[120]	3 days	30 days
	PedvaxHIB (Merck)[121]	3 days	3 days
	Hiberix (GSK)[122]	4 days	31 days
DTaP	Infanrix (GSK)[123]	8 days	28 days
	Daptacel (Sanofi)[124]	14 days	6 months
Poliovirus	Ipol (Sanofi)[125]	3 days	3 days

[115] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf (emphasis added)
[116] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf (emphasis added)
[117] https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf
[118] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm110114.pdf
[119] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm224503.pdf
[120] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109841.pdf
[121] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm253652.pdf
[122] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm179530.pdf
[123] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm124514.pdf
[124] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm103037.pdf
[125] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm133479.pdf

Pneumococcal	Prevnar 13 (Wyeth)[126]	7 days	6 months
Combination Vaccines	Pediarix (GSK)[127]	8 days	30 days + phone call at 6 months
	Pentacel (Sanofi)[128]	7 days	60 days + phone call at 6 months

Again, without a placebo controlled clinical trial, which none of the above had, the actual safety profile of each vaccine cannot be assessed even for the limited duration that its safety was reviewed. Moreover, even assuming placebo controls were used, tracking safety for (at most) a mere 6 months after injecting a 2-month old baby will not reveal if the vaccine caused autoimmune, neurological or developmental disorders that are likely to only be apparent or diagnosed after the child is a few years of age.

At *four months of life*, HHS's vaccine schedule instructs that babies again be injected with the Hib, DTaP, IPV, and PCV 13 vaccines.[129] The above table shows the issues with these vaccines' testing durations.

At *six months of life*, HHS's vaccine schedule instructs that babies again be injected with the Hepatitis B, Hib, DTaP, IPV, and PCV 13 vaccines.[130] In addition, HHS's schedule also lists the influenza vaccine already discussed above.[131]

As early as *twelve months of life*, HHS's vaccine schedule provides that babies again be injected with Hib and PCV13 vaccines, as well as receive the MMR, Varicella and Hepatitis A vaccines.[132] As for MMR, its package insert does not describe, as would be required by federal law, a single clinical trial of the MMR vaccine upon which its licensure is based.[133]

As for Varicella, its clinical trial, which used an injection of 45 mg of neomycin as a control (as discussed above), only assessed safety for a period of weeks.[134] As for the two Hepatitis A vaccines, solicited reactions for both were gathered for approximately two weeks and unsolicited reactions for approximately a month and Havrix conducted a six month non-obligatory follow-up telephone call.[135] Even this limited vaccine safety monitoring reveals nothing about the actual safety profile of these products since there was

[126] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm201669.pdf
[127] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM241874.pdf
[128] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm109810.pdf
[129] https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf
[130] https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf
[131] https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf
[132] https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf
[133] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123789.pdf. See footnote 31.
[134] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142812.pdf (Greater than 1 percent of children had one or more of these reactions: upper respiratory illness, cough, irritability/nervousness, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, contact rash, headache, malaise, abdominal pain, nausea, eye complaints, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions, stiff neck, heat rash/prickly heat, arthralgia, dermatitis, constipation, itching.)
[135] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224555.pdf
https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110049.pdf

no placebo control used in their clinical trials. And even if a placebo was used, a single six month follow-up phone call will not reveal the developmental, neurological or autoimmune issues that will only become apparent after a baby is at least a few years old.

In sharp contrast to the short safety testing periods for vaccines, most drugs have pre-licensure safety review periods which last years. For example, the drugs Enbrel[136], Lipitor[137], and Botox[138] had safety review periods of 6.6 years, 4.8 years and 51 weeks, respectively, and each had an actual placebo control group. And these drugs are typically for adults, not infants and children.

Moreover, even though safety review periods for vaccines typically lasted only days or weeks, the efficacy review period for vaccines often lasted years.[139] The "efficacy review" typically tracks antibody levels to assess how well the new vaccine will likely prevent the target infection. This review often lasts years because the biological changes in the body a vaccine seeks to achieve, typically production of vaccine strain antibodies, often require multiple injections over a period of months or years followed by monitoring efficacy for at least a few years.[140] Vaccine safety should be tracked at least as long as vaccine efficacy because it can take years for chronic conditions causally linked to or suspected to be caused by vaccines to become apparent. As HHS has explained: "because the childhood immunization schedule is essentially a long-term exposure, occurring over 18 to 24 months, long-term adverse events may be more biologically plausible than short-term events."[141]

Indeed, scientific findings, including by HHS, clearly refute the assumption that any adverse outcome of vaccination, especially when vaccinating babies during the first six months of life, will be apparent fairly immediately.[142] Yet this assumption underlies the design for assessing safety in the clinical trials relied upon to license pediatric vaccines. At the very least, since efficacy is already being tracked for years, safety should also be tracked for the same duration.

It is common sense that if HHS licenses vaccines without safety data extending beyond a few days, weeks or months, it is scientifically impossible to ascertain if babies will develop immunological, developmental or neurological disorders beyond these short safety review periods. There is no justifiable reason why HHS refuses to examine whether giving 29 vaccine doses by one year of age can lead to health issues at 5 years of age. As the Institute

---

[136] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf
[137] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf
[138] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf
[139] https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm
[140] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html; https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html For example, pursuant to HHS's vaccine schedules, every person is to receive a diphtheria containing vaccine at the following ages: 2-months, 4-months, 6-months, 15-months, 4-years, 11-years, and then every ten years until death.
[141] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[142] Ibid.; https://www.ncbi.nlm.nih.gov/pubmed/22235051

of Medicine admitted: science still does not know "if there is a relationship between [the numerous known] short-term adverse events following vaccination and long-term health issues."[143]

(ii) HHS's "Solicited" v. "Unsolicited" Scheme Further Conceals Actual Safety Profile

Moreover, unlike almost all drugs, HHS permits pharmaceutical companies to use preset lists of adverse reactions they ask their researchers to monitor and evaluate in vaccine clinical trials – so called "solicited" adverse reactions.[144] Asking about certain "solicited" adverse reactions undoubtedly creates a bias in favor of parents reporting those adverse reactions, rather than reporting "unsolicited," but more serious, adverse reactions. The reason for this approach appears to be that HHS and pharmaceutical companies are trying to institutionalize a few adverse events, such as injection site soreness, as the only adverse events that are caused by vaccination. This "don't ask, and hope they don't tell" policy is troubling.

Having a pre-set list of adverse reactions that are "solicited" by researchers institutionalizes and legitimizes HHS and the pharmaceutical industry's customary practice of accepting a very small number of minor reactions as being "caused" by vaccines. This allows the "unsolicited" reports made by subjects and their parents, many of which would likely fall outside the short review period, to be easily relegated to a broad wastebasket category, such as "new medical condition." This practice leaves the pharmaceutical industry entirely free and indeed highly likely to reject these "unsolicited" reactions as unrelated to vaccination or consider them idiosyncratic medical events based on a preexisting genetic predisposition or other latent tendency, and therefore "coincidental" and unrelated to the vaccine.

The problems created by the solicited vs. unsolicited categories are not merely abstract concerns. To the contrary, the trials conducted for the HPV vaccine, Gardasil, provide a ready example of how this dual category structure biases researchers against finding that unsolicited adverse reactions are caused by the vaccine. When Gardasil was tested for safety in clinical trials in Denmark, many participants repeatedly advised clinicians conducting the trials that after vaccination they could no longer engage in various basic life functions due to numerous brain and immune dysfunction symptoms.[145] These "unsolicited" Gardasil vaccine reactions, however, were discarded by the clinical trial researchers, who were paid by the pharmaceutical company seeking a license for Gardasil.[146]

---

[143] https://www.nap.edu/read/13563/chapter/5#45

[144] https://www.ncbi.nlm.nih.gov/pubmed/16231957 ("Spontaneous (unsolicited) collection of adverse event data is used in most pharmaceutical trials.")

[145] https://slate.com/health-and-science/2017/12/flaws-in-the-clinical-trials-for-gardasil-made-it-harder-to-properly-assess-safety.html

[146] https://slate.com/health-and-science/2017/12/flaws-in-the-clinical-trials-for-gardasil-made-it-harder-to-properly-assess-safety.html

The researchers could discard this data because, despite being an entirely new vaccine for a new disease, no placebo control was used.[147] As a result, the pharmaceutical company paid researchers used their "judgment," not the scientific method, to decide if any complications were related to the vaccine.[148]

Even more troubling, these researchers actually told women reporting serious life altering reactions that, "This is not the kind of side effects we see with this vaccine" – an inexplicable and unscientific response for researchers conducting clinical trials of a new vaccine.[149] The only reason this fact came to light was because of a thorough eight-month long investigation by Slate (a strongly pro-vaccine news outlet) which sought out and found the clinical trial patients and matched them with their clinical trial records.[150]

(iii) HHS Gives False Impression it Determines Whether Each Reported Adverse Reaction is Related to the Vaccine on Trial

As this incident with Gardasil shows, even if pediatric vaccine clinical trials did gather sufficient medical data to assess safety, the determination of whether an adverse event reported during the clinical trial is associated with the vaccine under review is left to the pharmaceutical company paid researchers conducting the clinical trial.[151] Nevertheless, HHS's letter seeks to mislead the reader by stating:

> Serious adverse events are always evaluated by FDA to determine potential association with vaccination regardless of their rate of incidence in the control group.[152]

However, because pharmaceutical companies and their paid researchers determine if each reported adverse event in a trial is related to the vaccine, HHS's assertion that "[s]erious adverse events are always evaluated by the FDA to determine potential association with vaccination" is disingenuous.

Ironically, if placebo control groups were used, then there would be no need for a case-by-case determination regarding whether each reported "unsolicited" adverse reaction is related to the vaccine under review. It is only because of the scientifically and morally

---

[147] https://slate.com/health-and-science/2017/12/flaws-in-the-clinical-trials-for-gardasil-made-it-harder-to-properly-assess-safety.html
[148] https://slate.com/health-and-science/2017/12/flaws-in-the-clinical-trials-for-gardasil-made-it-harder-to-properly-assess-safety.html
[149] https://slate.com/health-and-science/2017/12/flaws-in-the-clinical-trials-for-gardasil-made-it-harder-to-properly-assess-safety.html
[150] https://slate.com/health-and-science/2017/12/flaws-in-the-clinical-trials-for-gardasil-made-it-harder-to-properly-assess-safety.html
[151] For example, in the clinical trial for ActHIB there was no control group and 3.4% of the babies receiving this vaccine had a serious adverse event within 30 days of vaccination; HHS nonetheless licensed this vaccine because the trial investigators working for ActHIB's manufacturer decided none of them were related to the vaccine. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm109841.pdf ("within 30 days ... (3.4%) participants [babies] experienced a serious adverse event" but "[n]one was assessed by the investigators as related to the study of vaccines")
[152] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

defunct refusal to require placebo-controlled trials that there is a need to rely on the "judgment" of pharmaceutical company paid researchers to decide if the "unsolicited" adverse event is related to the vaccine.[153]

This adds a very dangerous bias into what is already unreliable (no placebo control) and limited (duration too short) safety data from vaccine clinical trials. Pharmaceutical companies have a powerful financial incentive to minimize any safety concerns to ensure licensure since they have almost no liability for vaccine injuries but yet stand to typically earn billions of dollars from each newly licensed pediatric vaccine. As explained by Dr. Marcia Angell[154], currently a professor in the Center for Bioethics, Harvard School of Medicine, and member of the Institute of Medicine, and former editor-in-chief of the New England Journal of Medicine:

> Clinical trials are also biased through designs for research that are chosen to yield favorable results for sponsors. … In short, it is often possible to make clinical trials come out pretty much any way you want, which is why it's so important that investigators be truly disinterested in the outcome of their work. …
>
> It is no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of *The New England Journal of Medicine*. …[155]

Dr. Angell also points out that, "Most of the big drug companies have settled charges of fraud," including GSK and Merck, explaining that the legal "costs, while enormous in some cases, are still dwarfed by the profits generated by these illegal activities, and are therefore not much of a deterrent."[156]

C. Conclusion to HHS's Claims Regarding Vaccine Clinical Trials

Best scientific research practices should not be bent or broken to allow HHS to approve pediatric vaccines. With all drugs, the pharmaceutical industry remains accountable for safety and liable in civil court for injuries caused by the drugs they put on the market. Hence, during pre-licensure clinical trials testing experimental drugs,

[153] The false and misleading claims regarding clinical trials undercut any basis for relying on the following conclusory assertion in HHS's letter: "*Please be assured that vaccine safety is carefully examined regardless of whether there is a placebo included in the clinicals trials*."
[154] http://bioethics.hms.harvard.edu/person/faculty-members/marcia-angell
[155] https://www.nybooks.com/articles/2009/01/15/drug-companies-doctorsa-story-of-corruption/
[156] https://www.nybooks.com/articles/2009/01/15/drug-companies-doctorsa-story-of-corruption/

pharmaceutical companies at least have a financial incentive to their shareholders to ascertain each drug's safety profile – to determine if its liability exposure exceeds its likely revenue stream – otherwise after licensure they could face losses that exceed the drug's expected sales. This is likely why pharmaceutical companies conduct long-term placebo-controlled trials before seeking licensure for even short-acting, minor or cosmetic prescription or over-the-counter drugs.[157]

In contrast, pharmaceutical companies do not have liability for injuries caused by most of their vaccine products. Therefore, in line with their fiduciary duty to their shareholders, they have a financial incentive to get a new vaccine licensed by HHS as fast as possible with as little review of the vaccine's safety profile as possible. Newly licensed or even longstanding vaccines recommended by HHS for routine use by all children, such as Gardasil, Prevnar 13, or MMR, generate billions of dollars in revenue annually.[158] If it turns out that the vaccine causes serious harm, and a parent can prove it in Vaccine Court (over the defense mounted by the DOJ representing HHS), the claim is paid by the Federal Government using funds obtained from an excise tax collected from vaccine consumers – not paid by pharmaceutical companies.[159] Thus, pharmaceutical companies have a financial disincentive to identify safety issues that would prevent licensure and literally no incentive to identify safety issues after licensure.

This is precisely why the 1986 Act, simultaneous with granting vaccine makers financial immunity, made HHS responsible for vaccine safety.[160] Yet, HHS has abandoned this duty by not requiring long-term placebo-controlled clinical trials. Without such trials, the actual safety profile of each pediatric vaccine, or any combination thereof, cannot be determined before they are – pursuant to HHS's childhood vaccine schedule – injected into millions of American children. Once that happens, HHS becomes utterly conflicted from funding or conducting research that may find that a vaccine HHS previously licensed and recommended does, in fact, cause significant harm to more than a few children.

Indeed, admitting after licensure that a vaccine causes a certain serious harm would eliminate HHS's ability to defend itself against claims alleging such harm in Vaccine Court, which could amount to billions or even trillions of dollars in financial liability. It would also tarnish HHS's reputation and reduce the public's trust in HHS because, unlike drugs, HHS spends billions of dollars annually purchasing, distributing and vigorously promoting childhood vaccines.[161] This creates a serious conflict of interest within HHS that prevents it

---

[157] For example, the weight loss drug, Belviq (only indicated for adult use), was safety tested in a placebo-controlled trial for two years before being licensed. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf

[158] https://investors.pfizer.com/financials/annual-reports/default.aspx; https://investors.merck.com/financials/sec-filings/default.aspx; https://www.gsk.com/media/4751/annual-report.pdf; https://www.sanofi.com/en/investors/reports-and-publications/

[159] 42 U.S.C. § 300aa-11; 42 U.S.C. § 300aa-15

[160] 42 U.S.C. § 300aa-11; 42 U.S.C. § 300aa-27

[161] https://www.hhs.gov/sites/default/files/fy2017-budget-in-brief.pdf?language=es

from rationally evaluating post-licensure reports of adverse events. It is therefore critical for HHS to have a clear and robust picture of the actual safety profile of each vaccine and the vaccination schedule *before* it is recommended and promoted by HHS to the public.

For example, Engerix B, manufactured by GSK, was originally licensed for children in the late 1980s based on an uncontrolled trial that only reviewed safety for five days (as discussed above).[162] Engerix B had to be reapproved by HHS almost twenty years later after the preservative used in the vaccine was changed.[163] The vaccine otherwise remained identical to what had been approved twenty years prior.[164] In the reapproval clinical trial report submitted by GSK to HHS in 2005, more than half of the babies reported an adverse event within 3 days of receiving this vaccine and 55 of the 587 babies in the study reported a serious adverse event.[165] That means 9.4% of the babies experienced a serious adverse event. Absent a placebo control group, however, it was left to GSK's paid researchers to decide whether these adverse events were caused by the vaccine.[166] Unsurprisingly, the GSK researchers declared the adverse events were not caused by its vaccine, and the vaccine was reapproved.[167] If HHS had overruled that finding, it could serve as an admission it previously licensed, recommended and widely promoted a vaccine that caused numerous serious adverse events in American babies, thereby creating buckling financial liability as well as serious reputational damage to HHS. This conflict makes it unlikely HHS will ever admit after licensure, due to at least willful blindness, that a vaccine causes any serious widespread harm.

This structural conflict at HHS is dangerous. There should be no compromise when it comes to the health of children, especially babies and newborns. The American public deserves nothing short of long-term placebo-controlled trials to know the true adverse event rate, without any bias.[168]

The bottom line is that when vaccines are licensed and recommended to be injected into every American child, apart from certain reactions, such as a sore arm, occurring within days of the vaccination, HHS does not know the safety profile of these products. As even HHS's own paid experts, the IOM, explain: "Because [vaccine] trials are primarily … for determination of efficacy, conclusions about vaccine safety derived from these trials are

---

[162] https://web.archive.org/web/20170723025206/http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM244522.pdf

[163] https://web.archive.org/web/20170723025206/http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM244522.pdf

[164] https://web.archive.org/web/20170723025206/http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM244522.pdf

[165] Ibid.

[166] Ibid.

[167] Ibid.

[168] This is in fact what the *Nuremberg Code* demands. https://history.nih.gov/research/downloads/nuremberg.pdf ("The voluntary consent of the human subject is absolutely essential. This means that the person … should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision.")

limited."[169] HHS apparently proceeds nonetheless to license, recommend and promote these products based on its *a priori* assumption of and belief in their safety. This should be concerning because if HHS's "belief" is incorrect, it could have negative consequences for the health of current and future generations of American children.

Please respond to all points above and answer the questions in Appendix A.

II. SAFETY OF INJECTING BABIES WITH HEPATITIS B VACCINE

In our opening letter, we asked that HHS "Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life."[170]

A. Safety Data for Hepatitis B Licensure is Plainly Deficient

HHS begins its response by stating: "Data relied upon in licensing infant use of hepatitis B vaccine is summarized in the respective package insert."[171] It is troubling that HHS responds to the above request by citing the package inserts when our opening letter explained that these precise package inserts provide that their safety was not monitored for longer than five days after injection.[172] As a result, HHS's response merely affirms the concerns we expressed in our original letter that the Hepatitis B vaccine was inadequately tested for safety prior to licensure.

Recombivax HB's package insert asserts it was deemed safe for children based on a clinical trial in which 147 infants and children (up to 10 years of age) were monitored for five days after vaccination.[173] This trial is useless for assessing the safety of this vaccine for pediatric use (let alone for babies on the first day of life) because the sample size is too small, the safety review period is too short, and there is no placebo control. The safety information in the package insert for Engerix-B is just as inadequate since the clinical trial for this vaccine also had no placebo control and only monitored safety for four days after vaccination.[174]

These package inserts plainly do not support the safety of administering these products to babies. Hence, HHS's assertion that the "Data relied upon in licensing infant use of hepatitis B vaccine is summarized in the respective package insert" is very troubling.

---

[169] https://www.nap.edu/read/13563/chapter/4
[170] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[171] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[172] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf
[173] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf
[174] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm224503.pdf

B. Safety of Hepatitis B Recommendation for Babies Plainly Deficient

Aside from the package inserts, HHS's response points to only one other identifiable document to support its claim that the Hepatitis B vaccine is safe for babies – a report from the Advisory Committee on Immunization Practices (**ACIP**) that HHS asserts it relied upon for its "recommendation for all children to receive these vaccines."[175] Sadly, as with the package inserts, this ACIP report does not support the safety of these vaccines for babies or children. A copy of the report is cited in a footnote to this sentence.[176]

The ACIP report cites seven studies to support its recommendation that every baby in this country receive Hepatitis B vaccine injections at 1-day, 1-month, and 6-months of life.[177] Two of the cited studies only included adult homosexual males and therefore provide no useful data to evaluate the safety of injecting newborns.[178] The third was a retrospective study that did not use either of the Hepatitis B vaccines licensed for infants in the United States, excluded children that did not complete the vaccine series and lacked a placebo control.[179] The fourth was a retrospective study of potential neurological events from the Hepatitis B vaccine based on reports submitted to a passive surveillance system.[180] This study is also useless for assessing the safety of administering the Hepatitis B vaccine to infants because the study involved "virtually all" adults and did not provide any separate results for infants or children.[181] Moreover, its conclusions regarding safety are pure speculation because, as study authors explained, "underreporting is a well-recognized problem of such surveillance systems" and the "magnitude of underreporting of neurological events after hepatitis B vaccination is unknown."[182] This once again drives home the need for a placebo-controlled trial for each pediatric vaccine prior to licensure.

The three remaining studies relied upon to support the safety of the Hepatitis B vaccine cited in the ACIP report were clinical trials. But none of these clinical trials are useful for understanding the safety of injecting Hepatitis B vaccine into babies.[183] First, none of them had a placebo control.[184] Second, none of these trials assessed safety for longer than seven days after vaccination.[185]

---

[175] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[176] https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm
[177] https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm
[178] https://www.ncbi.nlm.nih.gov/pubmed/6810736; https://www.ncbi.nlm.nih.gov/pubmed/6997738
[179] Chen D-S. Control of hepatitis B in Asia: mass immunization program in Taiwan. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:716-9.
[180] https://www.ncbi.nlm.nih.gov/pubmed/2962488
[181] https://www.ncbi.nlm.nih.gov/pubmed/2962488
[182] https://www.ncbi.nlm.nih.gov/pubmed/2962488
[183] https://www.ncbi.nlm.nih.gov/pubmed/2952812; https://www.ncbi.nlm.nih.gov/pubmed/2943814; https://www.ncbi.nlm.nih.gov/pubmed/2528292
[184] https://www.ncbi.nlm.nih.gov/pubmed/2952812; https://www.ncbi.nlm.nih.gov/pubmed/2943814; https://www.ncbi.nlm.nih.gov/pubmed/2528292
[185] https://www.ncbi.nlm.nih.gov/pubmed/2952812; https://www.ncbi.nlm.nih.gov/pubmed/2943814; https://www.ncbi.nlm.nih.gov/pubmed/2528292

Indeed, one study had 122 infants and monitored safety for only 7 days.[186] Another study had 79 children monitored for 5 days.[187] Remarkably, in this study 18 percent of the children experienced a systemic or serious adverse reaction (fatigue/weakness, diarrhea, etc.), but, absent a placebo control, the pharmaceutical company paid researchers were left to decide whether or not these reactions were related to the vaccine.[188] The final study had 3,000 infants and children but *only* monitored safety on the day of and the third day after vaccination.[189] As HHS is well aware, autoimmune, neurological and developmental disorders will often not be diagnosed until after babies are a few years old.[190] The ACIP report even acknowledges that "systematic surveillance for adverse events [in infants] has been limited."[191]

As this shows, even though we asked for the science to support the safety of injecting every newborn with the Hepatitis B vaccine starting on the first day of life, the studies HHS has provided do not support such safety and would not be sufficient to license these products for veterinary use in farm animals. For example, prior to licensure of a vaccine for use in chickens, "Daily observation records are required for at least 21 days after vaccination."[192]

C. Urgent Need for Placebo-Controlled Trial of Hepatitis B Vaccine

The need to assess the safety of each Hepatitis B vaccine in robust clinical trials is manifest. The following is a list of the reported post-marketing adverse reactions added to the package insert for Engerix-B because Merck had a "basis to believe there is a causal relationship between the drug and the occurrence of the adverse event"[193]:

> Abnormal Liver Function Tests; Allergic Reaction; Alopecia; Anaphylactoid Reaction; Anaphylaxis; Angioedema; Apnea; Arthralgia; Arthritis; Asthma-Like Symptoms; Bell's Palsy; Bronchospasm; Conjunctivitis; Dermatologic Reactions; Dyspepsia; Earache; Eczema; Ecchymoses; Encephalitis;

[186] https://www.ncbi.nlm.nih.gov/pubmed/2952812
[187] https://www.ncbi.nlm.nih.gov/pubmed/2943814
[188] https://www.ncbi.nlm.nih.gov/pubmed/2943814
[189] https://www.ncbi.nlm.nih.gov/pubmed/2528292
[190] For example, according to the CDC, even for a common neurological disorder such as ADHD, "5 years of age was the average age of diagnosis for children reported as having severe ADHD." https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html As another example, learning disabilities, a group of common developmental issues, are often "identified once a child is in school." https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed Even asthma, a very common autoimmune condition, whose symptoms are obvious, for children under 5 years of age "diagnosis can be difficult because lung function tests aren't accurate before 5 years of age" and "[s]ometimes a diagnosis can't be made until later, after months or even years of observing symptoms." https://www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513
[191] https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm
[192] https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_204.pdf
[193] 21 C.F.R. 201.57

> Encephalopathy; Erythema Multiforme; Erythema Nodosum; Guillain-Barré Syndrome; Hypersensitivity Syndrome (serum sickness-like with onset days to weeks after vaccination); Hypoesthesia; Keratitis; Lichen Planus; Meningitis; Migraine; Multiple Sclerosis; Myelitis; Neuritis; Neuropathy; Optic Neuritis; Palpitations; Paralysis; Paresis; Paresthesia; Purpura; Seizures; Stevens-Johnson Syndrome; Syncope; Tachycardia; Tinnitus; Transverse Muscular Weakness; Thrombocytopenia; Urticaria; Vasculitis; Vertigo; Visual Disturbances.[194]

And these are the reported post-marketing adverse reactions for Recombivax HB added to its package insert because GSK had a basis to conclude each has a causal relationship with that vaccine:

> Agitation; Alopecia; Anaphylactic/Anaphylactoid Reactions; Arthralgia; Arthritis; Arthritis Pain In Extremity; Autoimmune Diseases; Bell's Palsy; Bronchospasm; Constipation; Conjunctivitis; Dermatologic Reactions; Ecchymoses; Eczema; Elevation Of Liver Enzymes; Encephalitis; Erythema Multiforme; Erythema Nodosum; Exacerbation Of Multiple Sclerosis; Febrile Seizure; Guillain-Barré Syndrome; Herpes Zoster; Hypersensitivity Reactions; Hypersensitivity Syndrome (serum sickness-like with onset days to weeks after vaccination); Hypesthesia; Increased Erythrocyte Sedimentation Rate; Irritability; Lupus-Like Syndrome; Migraine; Multiple Sclerosis; Muscle Weakness; Myelitis Including Transverse Myelitis; Optic Neuritis; Peripheral Neuropathy; Petechiae; Polyarteritis Nodosa; Radiculopathy; Seizure; Stevens-Johnson Syndrome; Somnolence; Syncope; Systemic Lupus Erythematosus (SLE); Tachycardia; Thrombocytopenia; Tinnitus; Urticaria; Urticaria; Uveitis; Vasculitis; Visual Disturbances.[195]

These post-marketing reactions reveal a consistent pattern of autoimmune, neurological and other chronic disorders that would appear or only be diagnosed years after vaccinating a baby. Nevertheless, instead of investigating these adverse events in methodologically sound clinical trials, HHS responds to these post-marketing reports of chronic life-long injuries by saying that "causation has not been proven," knowing full well that causation is highly unlikely to be proven, one way or another, until a placebo-controlled trial of sufficient duration is conducted.

---

[194] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm224503.pdf
[195] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm110114.pdf

By approving, recommending and aggressively promoting use of the Hepatitis B vaccine for all infants, HHS created a liability-free captive market for Merck and GSK by ensuring millions of babies every year will be injected with their Hepatitis B products. Since HHS's recommendation in 1991 for the universal pediatric use of these products, these companies have generated over $10 billion in sales from this vaccine.[196] Yet, HHS's response makes clear that it lacked the clinical trial safety data necessary to support its licensure and aggressive marketing of this product for use in all babies.

It is deeply troubling that, despite repeated assurances by HHS that the safety science for this vaccine is robust and complete, when we demanded to actually see this science, HHS was unable to produce it because it apparently does not exist.

Please respond to the above and the specific questions listed in Appendix A.

III. THE VACCINE ADVERSE EVENT REPORTING SYSTEM

Between 2013 and 2018, the Vaccine Adverse Event Reports System (**VAERS**), operated by HHS, has received 261,294 reports of adverse vaccine events, including 2,081 deaths, 5,477 permanent disabilities, and 20,778 hospitalizations.[197] As HHS is aware, "fewer than 1% of vaccine adverse events are reported" because reporting to VAERS is voluntary.[198] We therefore asked in our opening letter why, after Harvard developed a system for spontaneously creating vaccine adverse event reports, "HHS failed to cooperate with Harvard to automate VAERS reporting?"[199] HHS's response does not answer this question.

In 2006, an HHS agency, the Agency for Healthcare Research and Quality, provided a $1 million grant to create a spontaneous reporting system to VAERS at Harvard Pilgrim Health Care.[200] The result was the successful creation of a system at Harvard Pilgrim which automatically created adverse vaccine event reports:

> Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions … were identified.[201]

[196] https://www.thomsonone.com/
[197] https://wonder.cdc.gov/vaers.html
[198] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[199] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[200] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[201] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf

After automating the spontaneous creation of adverse event reports at Harvard Pilgrim, its developers asked the CDC to take the final step of linking VAERS with the Harvard Pilgrim system so that these reports could be automatically transmitted into VAERS.[202] One would expect the CDC to rush to take this final step given that the preliminary data from this project showed that over only a three-year period, there were 35,570 reportable reactions in just 376,452 vaccine recipients.[203] Instead, the CDC refused to cooperate. As the Harvard researchers explained:

> Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.[204]

Given HHS's statutory mandate to assure safer vaccines, it should have moved forward quickly with implementing the spontaneous VAERS reporting system developed by Harvard -- not refused to even communicate with the Harvard Medical School researchers being funded by HHS.

We therefore asked why HHS did not cooperate in implementing the spontaneous VAERS reporting system, and HHS's response incongruously states that doctors may "submit reports directly online" or "download and complete the writable and savable VAERS 2.0 form and submit it using an electronic document upload feature."[205] This does not answer our question. Nor does it address the basic issue that VAERS is a voluntary passive reporting system and history has shown that clinicians do not fill out VAERS reports with any regularity, resulting in only a minuscule number of adverse vaccine events being reported.[206] It also does not correct the problem that VAERS is a passive reporting system, thus limiting its usefulness in making determinations about vaccine safety.[207] The fact that HHS has refused to automate this process leads to the question of whether the decision to keep VAERS as a passive reporting system is intentional in order to hamper its ability to provide reliable information regarding the rate at which a given injury occurs after a given vaccine.

These issues with VAERS have been highlighted for over 30 years and could be easily addressed by implementing automated reporting systems at hospitals and health clinics so

---

[202] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[203] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[204] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[205] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[206] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf "Reasons for clinical under-reporting might include failure to associate an acute health event to recent vaccines, lack of awareness of VAERS, the misperception that only serious events should be reported, and lack of time to report." https://www.ncbi.nlm.nih.gov/pubmed/26060294 (cited by HHS)
[207] https://vaers.hhs.gov/about.html; https://vaers.hhs.gov/data/dataguide.html

that reports are electronically generated based on patients' medical records and submitted to VAERS automatically. This would also assure reporting from a known sample size and thus convert VAERS from a passive to an active reporting system, thereby permitting more reliable conclusions to be drawn from the analysis of the VAERS database. But, as discussed above, the CDC refused to cooperate with Harvard to implement such a system in 2007.

The 2015 study cited in HHS's letter shows that HHS continues to refuse to cooperate to implement an automated system.[208] HHS claims that this three-year-old study shows that the "CDC is developing the next generation of spontaneous reporting mechanisms for the VAERS."[209] This claim is at best disingenuous.

The program described in this 2015 study, which the CDC created to generate "spontaneous reporting," makes clear the CDC is desperate to avoid any actual spontaneous reporting.[210] Despite the fact that this program does spontaneously generate vaccine adverse events reports from patients' medical records, the CDC does not permit this program to automatically submit these reports to VAERS.[211] Instead, it emails each report to the patient's doctor and asks the doctor to review and decide whether to submit the report to VAERS.[212] This requirement is backwards.

The purpose of VAERS is to identify previously unknown associations between a vaccine and a condition (ICD-9/10 code). A doctor will, of course, be unlikely to affirm that a reaction is related to a vaccine without a known clinical precedent, the very evidence VAERS is intended to compile. Unsurprisingly, in the eight-month period it tested this new program, the system generated 1,385 vaccine adverse event reports but doctors who received these reports only clicked to submit a grand total of 16 of them to VAERS.[213]

Moreover, the CDC designed this program to even prevent it from generating reports for any conditions (ICD-9/10 code) the CDC predetermined are not associated with a vaccine.[214] The CDC also prevents the program from generating any reports for an adverse event or health condition that the patient had experienced prior to vaccination, thereby eliminating reports of any instance where the vaccine worsened or caused a relapse of a preexisting condition.[215] Hence, the *only* reports the program can generate are for adverse events the CDC deems permissible to associate with a vaccine.[216]

---

[208] https://www.ncbi.nlm.nih.gov/pubmed/26060294
[209] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[210] https://www.ncbi.nlm.nih.gov/pubmed/26060294
[211] https://www.ncbi.nlm.nih.gov/pubmed/26060294
[212] https://www.ncbi.nlm.nih.gov/pubmed/26060294
[213] Doctors failed to transmit reports reflecting harms that even HHS accepts are caused by vaccines; doctors affirmatively selected to not transmit 209 reports, which reflects the institutionalized belief about what injuries are caused by vaccines; and for the remaining 1,176 reports, nearly 85% of all reports, there was no clinical response. https://www.ncbi.nlm.nih.gov/pubmed/26060294
[214] https://www.ncbi.nlm.nih.gov/pubmed/26060294
[215] https://www.ncbi.nlm.nih.gov/pubmed/26060294
[216] https://www.ncbi.nlm.nih.gov/pubmed/26060294

In short, the CDC has assured that its vaccine reaction reporting program will only generate reports for injuries the CDC deems acceptable to associate with a vaccine, and then creates the hurdle of requiring busy clinicians to review and click to affirmatively submit a report, which they are highly unlikely to do for the reasons discussed above.

When one considers that the CDC long-ago developed and championed the use of electronic systems that track the movement of each vaccine from its manufacture to its administration, as well as the vaccination status of every child in each state, there is little excuse for not similarly championing the use of long ago developed programs for automatically generating and transmitting adverse reactions reports to VAERS.[217]

We therefore ask – again – for HHS to explain "why HHS failed to cooperate with Harvard to automate VAERS reporting?" as well as address the issues raised above and provide responses to the specific questions in Appendix A.

IV. VACCINE-INJURY PAIRS IN 1994 AND 2011 IOM REPORTS

In our opening letter, we asked HHS to provide the studies it has conducted to determine if there is a causal relationship between vaccination and what HHS claims are the 173 most commonly claimed injuries following vaccination.[218]

HHS's answer points to a recent 740-page review it conducted in 2014, entitled *Safety of Vaccines Used for Routine Immunization in the United States*, which HHS claims is "the most comprehensive review to date of published studies on the safety of routine vaccines recommended for children in the United States."[219] However, this report simply reaffirms that HHS has still not conducted studies to determine whether almost any of the 173 most commonly claimed injuries from vaccines (as determined by HHS) are caused by vaccines.

Worse, as discussed below, this 2014 "comprehensive review" of vaccine safety by HHS reveals that HHS does not understand the actual safety profile of its childhood vaccine schedule.

A. HHS's Paid Expert, the IOM, Finds Vaccine Safety Has Been Neglected

In 1991 and 1994, at HHS's request and in compliance with a congressional mandate in the 1986 Act, the Institute of Medicine (**IOM**) of the National Academy of Sciences appointed committees to examine the scientific literature and other evidence that could

[217] https://www.cdc.gov/vaccines/programs/vtrcks/about.html; https://www.cdc.gov/vaccines/programs/iis/index.html
[218] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[219] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

either prove or disprove a causal link between commonly reported serious health problems following administration of vaccines recommended by HHS for children. The first report, *Adverse Effects of Pertussis and Rubella Vaccines*, was published in 1991, and the second report, *Adverse Effects Associated with Childhood Vaccines*, was published in 1994.

The 1994 report evaluated 54 commonly reported serious injuries and vaccination for Diphtheria, Tetanus, Measles, Mumps, Polio, Hepatitis B, and Hib.[220] The IOM located sufficient science to support a causal connection between these vaccines and 12 serious injuries, including death, thrombocytopenia, and GBS.[221] The IOM, however, found that the scientific literature was insufficient to conclude whether or not these vaccines caused 38 other commonly reported serious injuries, including:

> Arthritis, Aseptic Meningitis, Demyelinating diseases of the central nervous system, Insulin-Dependent Diabetes Mellitus, Myelitis, Neuropathy, Residual Seizure Disorder, Sensorineural Deafness, Sudden Infant Death Syndrome, Sterility, Transverse Optic Neuritis[222]

The IOM lamented that: "The lack of adequate data regarding many of the adverse events under study was of major concern to the committee. Presentations at public meetings indicated that many parents and physicians share this concern."[223]

Fifteen years later, in 2011, HHS paid the IOM to review the available science regarding whether there is a causal relationship between vaccination and what HHS asserted are the 158 most common injuries claimed to occur from vaccines for Varicella, Hepatitis B, Tetanus, Measles, Mumps, and Rubella.[224] The IOM located science to support a causal relationship with 18 of these injuries, including pneumonia, meningitis, MIBE, and febrile seizures.[225] The IOM, however, found the scientific literature insufficient to conclude whether or not those vaccines caused 135 other serious injuries commonly reported after their administration, including:

> Acute Disseminated Encephalomyelitis, Afebrile Seizures, Amyotrophic Lateral Sclerosis, Arthralgia, Autoimmune Hepatitis, Brachial Neuritis, Cerebellar Ataxia, Chronic Headache, Chronic Inflammatory Demyelinating Poly-neuropathy, Chronic Urticaria, Encephalitis, Encephalopathy,

[220] https://www.nap.edu/read/2138/chapter/2#12
[221] https://www.nap.edu/read/2138/chapter/2#12
[222] https://www.nap.edu/read/2138/chapter/2#12
[223] https://www.nap.edu/read/2138/chapter/12
[224] https://www.nap.edu/read/2138/chapter/12
[225] https://www.nap.edu/read/13164/chapter/2#3

> Erythema Nodosum, Fibromyalgia, Guillain-Barré Syndrome, Hearing Loss, Immune Thrombocytopenic Purpura, Infantile Spasms, Juvenile Idiopathic Arthritis, Multiple Sclerosis, Neuromyelitis Optica, Optic Neuritis, Polyarteritis Nodosa, Psoriatic Arthritis, Reactive Arthritis, Rheumatoid Arthritis, Seizures, Small Fiber Neuropathy, Stroke, Sudden Infant Death Syndrome, Systemic Lupus Erythematosus, Thrombocytopenia, Transverse Myelitis[226]

Thus, out of the 158 most common serious injuries claimed to have been caused by one or more of these vaccines, the IOM found that for over 86% of those the science simply had not been performed to determine if there is a causal relationship between the vaccine and the injury.[227]

We therefore asked in our opening letter for HHS to identify the studies it has undertaken to determine whether there is a causal relationship between the 173 vaccine-injury pairs for which this question remained unanswered in the 1994 and 2011 IOM Reports.

B. HHS's "Comprehensive Review" of Vaccine Safety is Deeply Troubling

To support it has studied these vaccine-injury pairs, HHS, as noted above, points to its 2014 review entitled *Safety of Vaccines Used for Routine Immunization in the United States*.[228] But, the 2014 HHS review reached the same conclusion that there is insufficient evidence to conclude whether – save for four – there is a causal relationship between the 173 vaccine-injury pairs from the 1994 and 2011 IOM Reports.[229] It is therefore incredible that HHS would cite this report as proof it has conducted the scientific studies necessary to rule out or confirm a causal relationship for these vaccine injury pairs.

Far more troubling, if the 2014 HHS review is "the most comprehensive review" of the published literature on vaccine safety, as HHS claims, then this review should cause grave concern within HHS and the public regarding vaccine safety.

First, this so-called "comprehensive" review only looked at certain narrow vaccine-injury pairs pre-selected by HHS.[230] This narrow approach reveals nothing about the actual safety profile of these pediatric vaccines on HHS's childhood vaccine schedule. The only

---

[226] https://www.nap.edu/read/13164/chapter/2#3
[227] https://www.nap.edu/read/13164/chapter/2#3
[228] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[229] https://www.ncbi.nlm.nih.gov/books/NBK230053/ (HHS's 2014 review also added the following vaccine-injury pairs to the list of what it asserts are the most commonly claimed vaccine injuries: spontaneous abortion from HPV vaccine and meningitis from MMR vaccine.)
[230] https://www.ncbi.nlm.nih.gov/books/NBK230053/

way to actually know the true safety profile of HHS's childhood vaccine schedule or any individual vaccine on that schedule is a placebo-controlled trial of sufficient size and duration. This could provide an actual safety profile of each pediatric vaccine and HHS's childhood vaccine schedule. Instead of this basic trial design used for all drugs to understand their safety profile, HHS's approach is to work backwards by putting forth a self-selected smattering of vaccine-injury pairs, and if HHS cannot find a study proving the vaccine causes the injury (because no study was performed or adequately designed to find a causal relationship), it deems the vaccine safe.[231] This approach entirely ignores the scientific method and is transparently unsound because it begins with the *a priori* assumption that vaccines are safe and then relies upon a "comprehensive review" of self-selected, scarce and incomplete post-licensure vaccine literature to validate this assumption if it cannot find proof of harm.[232]

Second, after HHS assumed safety and narrowed the review to certain vaccine-injury pairs, the review then eliminated almost all studies showing that vaccines cause harm by excluding 20,312 of the 20,478 studies it identified as related or potentially related to vaccine safety.[233] The handful of studies that HHS did include for review were overwhelmingly studies in which a pharmaceutical company funded and/or authored (usually both) a review of its own vaccine.[234]

For example, it excluded all individual case reports despite the fact that practitioners can typically only afford to publish (typically instances of immediate and obvious vaccine injuries) in this form.[235] HHS excluded all experimental studies which could actually explain the biological mechanisms of how vaccines can cause injury or death.[236] HHS even excluded animal studies which – because experimentation with animals does not have ethical restrictions applicable to human research – often provide the best available scientific evidence of how vaccines can harm immune function, the brain and other tissue.[237]

The result is that this review included only 97 studies that are applicable to children[238], 77 of which were directly funded and/or authored (typically both) by the very vaccine manufacturer whose vaccine(s) the study reviews.[239] As for the remaining 20 studies, almost all were funded and/or authored by agencies and/or individuals that directly or indirectly receive funding from the manufacturer whose vaccine(s) the study reviews.[240]

---

[231] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[232] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[233] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[234] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[235] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[236] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[237] https://www.ncbi.nlm.nih.gov/books/NBK230053/ (HHS also excluded all studies using VAERS, one of the few resources available to study vaccine safety without pharmaceutical type funding.)
[238] The 2014 HHS review lists the study, Zaman K. et al. (2012), twice in Table 22 and the study, Khatun S. et al. (2012), twice in Table 25.
[239] https://www.ncbi.nlm.nih.gov/books/NBK230053/
[240] https://www.ncbi.nlm.nih.gov/books/NBK230053/

For example, HHS *excluded* an actual randomized, double-blind, placebo-controlled study which compared the rate of respiratory infections between controls receiving a placebo (saline injection) and subjects receiving inactivated influenza vaccine (**TIV**).[241] This non-pharma-funded nine-month study carefully tracked influenza-like illness symptoms through "symptom diaries and telephone calls," and "illness reports in any household member triggered home visits, during which nasal and throat swab specimens were collected."[242] The result:

> There was no statistically significant difference in the risk of confirmed seasonal influenza infection between recipients of TIV or placebo. … However, participants who received TIV had higher risk of ARI [acute respiratory illness] associated with confirmed noninfluenza respiratory virus infection (RR, 4.40; 95% CI, 1.31–14.8).[243]

This meant both groups had a similar rate of influenza, but the vaccinated group had 440% more cases of noninfluenza acute respiratory illness.[244] It appears that getting the flu shot may have significantly "reduced immunity to noninfluenza respiratory viruses."[245]

While this well designed and executed study reflecting serious negative impact of vaccination on health was *excluded* from HHS's comprehensive vaccine safety review, this review *included* a study funded by GSK and conducted by GSK employees which nonsensically compared 199 infants receiving PHiD-CV, DTPa, HBV, IPV and Hib (test group) with 101 infants receiving DTPa, HBV, IPV and Hib (control group).[246] Ironically, this study found that 4.5% of test infants and 5.9% of control infants had one or more serious adverse reactions following vaccination, but HHS accepted GSK's unsubstantiated and self-serving conclusion that none were "considered to be causally related to [GSK's] vaccination."[247]

Third, having limited the review of vaccine safety for children to 97 studies, HHS then claims that 59 of these studies compared "vaccinated versus unvaccinated children or adolescents"[248] The following is a break-down of these 59 studies by vaccine type: Rotavirus (34 studies), HPV (13 studies), Influenza (6 studies), Hib (3 studies), Meningococcal (2

---

[241] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[242] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[243] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[244] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[245] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[246] https://www.ncbi.nlm.nih.gov/pubmed/23432812
[247] https://www.ncbi.nlm.nih.gov/pubmed/23432812
[248] https://www.ncbi.nlm.nih.gov/books/NBK230053/

studies), and Varicella (1 study).[249] We commend HHS for making clear it understands there is a critical importance of comparing vaccinated and unvaccinated children to scientifically evaluate and understand vaccine safety. It is, however, unfortunate that HHS mislabels these studies as comparing "vaccinated versus unvaccinated children or adolescents" when the unvaccinated cohort is not really unvaccinated.[250]

For example, HHS lists two studies involving the meningococcal vaccine as comparing "vaccinated versus unvaccinated children."[251] However, in one study the test group and control group both received a meningococcal vaccine, and in the other study the test group received seven vaccines and the control group received six vaccines.[252] Claiming these two studies compared "vaccinated versus unvaccinated children" is misleading. The following table details these two studies and highlights the rate of serious adverse events (**SAE**s) that are ignored because the control group, wrongly labeled "unvaccinated," is used as the baseline for what is deemed "safe":

Vaccine & Manufacturer	Funding	Study	Test Group	Control Group	Finding
Meningococcal MCV4 (**Sanofi**)	Funded by **Sanofi** & authors include **Sanofi** employees	Khalil, M. et al. 2012 (Saudi Arabia)	MCV4 (151 children who received MPSV4 as babies)	MCV4 (85 children who did not receive MPSV4 as babies)	1.3% and 2.4% of the children in the subject and control group, respectively, had a serious adverse reaction (**SAE**)
Meningococcal MenACWY (**Novartis**)	Funded by **Novartis** & authors include **Novartis** employees	Klein, N.P. et al. 2012 (Three countries)	MenACWY, DTaP, IPV, Hib, HBV, IPV, PCV7, RV, V & MMRII (≈1000 babies)	DTaP, IPV, Hib, HBV, IPV, PCV7, RV, V & MMRII (≈500 babies)	75% of subject and 76% of control babies had an AE and "SAEs were reported with similar frequency among groups"

Similarly, the following table summarizes every purported "vaccinated versus unvaccinated" study that HHS could identify regarding the Hib vaccine (injected per HHS at 2, 4, 6 and 12 months of age) and again highlights the rate of serious adverse events that are ignored because the control group, wrongly labeled "unvaccinated," is used as the baseline for what is deemed "safe":

Vaccine & Manufacturer	Funding	Study	Test Group	Control Group	Finding
Hib - OPMC (**Merck**)	Funded by **Merck** & authors include **Merck** employees	Santosham M. et al., 1991 (U.S.)	OPMC, DTP, and OPV (2,588 infants)	DTP and OPV (2,602 infants)	4% of infants in each group were hospitalized within 30 days of vaccination
Hib - PHiD-CV (**GSK**)	Funded by **GSK** & authors include **GSK** employees	Huu, T.N. et al. 2013 (Vietnam)	PHiD-CV, DTPa, HBV, IPV & Hib (199 infants)	DTPa, HBV, IPV & Hib (101 infants)	4.5% and 5.9% of infants in the subject and control groups, respectively, reported a SAE

[249] https://www.ncbi.nlm.nih.gov/books/NBK230053/

[250] The rotavirus vaccine is given orally, not injection, and hence not considered. Nonetheless, the 35 rotavirus studies HHS states compare "vaccinated with unvaccinated children" actually compare children receiving oral drops of rotavirus with children receiving oral drops of the following vaccine ingredients: Polysorbate 80, Sucrose, Citrate, Phosphate, Dextran, Sorbitol, Amino acids, Dulbecco's Modified Eagle Medium, Calcium Carbonate, and/or Xanthan. https://www.ncbi.nlm.nih.gov/books/NBK230057/table/results.t19/?report=objectonly

[251] https://www.ncbi.nlm.nih.gov/books/NBK230053/

[252] https://www.ncbi.nlm.nih.gov/books/NBK230053/

Hib - PRP-OMP, POP-T, and HbOC (various)	No conflicts declared	Capeding M. R. Z. et al.,1996 (Philippines)	Hib, BCG, OPV, DTP and HBV (130 infants)	BCG, OPV, DTP and HBV (44 infants)	Admits that because "vaccines were administered simultaneously with other … vaccines … it is not possible to attribute the systemic reactions to any individual vaccine used in the study."

Similarly, for the six influenza vaccine studies listed by HHS as comparing "vaccinated with unvaccinated children," only four involved an injection of influenza vaccine,[253] and only one of these can be properly labeled as comparing "vaccinated with unvaccinated children." This one placebo-controlled study involved HIV-infected children and, while it provided almost no useful safety data because it only monitored safety for three days, it demonstrates that it is ethically permissible to use a saline placebo in a vaccine trial.

Vaccine & Manufacturer	Funding	Study	Test Group	Control Group	Finding
Flu - TIV (**Sanofi**)	Funded by **Sanofi** and authors include **Sanofi** employees	Englund J. A. et al., 2010 (U.S.)	TIV, DTaP, Hib, PNC, IPV, & HepB (915 babies)	Placebo, DTaP, Hib, PNC, IPV & HepB (460 babies)	Only collected "SAEs using previously defined criteria," yet within 28 days 1.9% of subject and 1.5% of control babies had a SAE
Flu – TIV (unknown)	None disclosed	Gotoh K. et al., 2011 (Japan)	TIV or no TIV (38 liver transplant recipients)	TIV (63 healthy children)	Safety not compared between subject and control groups
Flu - TIV (**Sanofi**)	None disclosed	Greenhawt, M.J. et al. 2012 (U.S.)	TIV (14 children)	TIV thirty minutes after saline injection (17 children)	Both groups had comparable adverse event rates
Flu - Vaxigrip (**Sanofi**)	Sponsored by Bristol- Myers Squibb	Madhi, S.A. et al. 2013 (South Africa)	TIV (203 HIV infected children)	Placebo - Saline (200 HIV-infected children)	Adverse events only collected for 3 days post-vaccination

As for the 13 studies regarding HPV vaccine labeled by HHS as "vaccinated versus unvaccinated," all – except for one study with a control group of 17 HIV-positive girls – use other vaccines or an injection of the aluminum adjuvant contained in the HPV vaccine as a control.[254] The table below reveals high rates of serious injuries and chronic illness reported by the HPV vaccine recipients, which were dismissed as not being a vaccine safety issue because the rates were similar to those reported in the "spiked" control group. It is noteworthy that unlike most of the vaccines in the tables above, the HPV vaccines were studied in adolescent and older women who, unlike children or babies, are able to clearly express if they are experiencing a serious adverse reaction, such as neurological issues.

[253] Two studies involved LAIV administered via nasal spray. In both, a pharmaceutical company reviewed its own product. One involved 20 immunocompromised children with cancer in which 10 received LAIV and 10 received a placebo with .5 mL of sucrose-phosphate buffer and no SAEs were reported since the pharmaceutical company's funded researchers did not consider them related to LAIV. (Halasa N. et al., 2011 (U.S.).) The other compared 261 children receiving LAIV with 65 children receiving placebo of .5 mL sucrose-phosphate buffer and being offered LAIV after 28 days which negated reaching safety conclusions. (Mallory R. M. et al.,2010 (U.S.).)

[254] https://www.ncbi.nlm.nih.gov/books/NBK230053/

Vaccine & Manufacturer	Funding	Study	Test Group	Control Group	Finding
HPV - Gardasil (**Merck**)	Funded by **Merck** and authors include **Merck** employees	Moreira Jr E. D. et al.,2011 (18 countries)	Gardasil (2,020 boys and men)	225 ug of AAHS (2,029 boys and men)	"systemic AE was generally comparable between the vaccine and placebo group (31.7% vs. 31.4%, respectively)"
HPV - Cervarix (**GSK**)	Funded by **GSK** and authors include **GSK** employees	Roteli-Martins C. M. et al., 2012 (Brazil)	Cervarix (223 girls and women)	500 ug Aluminum Hydroxide (213 girls and women)	24.6% of subjects and 15.5% of controls had a SAE, new onset of chronic disease or medically significant condition
HPV - Cervarix (**GSK**)	Funded by **GSK** and authors include **GSK** employees	Schwarz, T.F. et al. 2012 (5 countries)	Cervarix (1,035 girls)	Havrix and, after delay, Cervarix (1,032 girls)	38.8% of subjects and 32.4% of controls had a SAE, new onset of chronic disease or medically significant condition
HPV – Cervarix (**GSK**)	Funded by **GSK** and authors include **GSK** employees	Sow, P. S. et al. 20131 (Africa)	Cervarix (450 girls and women)	500 ug Aluminum Hydroxide (226 girls and women)	75.2% of subjects and 69.3% of controls reported a "Medically significant condition"
HPV - Gardasil (**Merck**)	Funded by **Merck** and authors include **Merck** employees	Block S. L. et al., 2010 (global)	Gardasil (11,792 people aged 9-23)	AAHS (9,092 aged 16-23) Gardasil minus AAHS and antigens (596 aged 9-15)	Between 9% and 14% of subjects and controls each had vaginal candidiasis, bacterial vaginosis, urinary tract infection and vaginal discharge
HPV - Cervarix (**GSK**)	Funded by **GSK** and authors include **GSK** employees	De Carvalho N. et al., 2010 (Brazil)	Cervarix (222 women)	500 ug Alumi-num Hydroxide (211 women)	9.9% of subjects and 8.6% of controls had a SAE or medically significant AE
HPV - Gardasil (**Merck**)	Funded by **Merck** and authors include **Merck** employees	Giuliano A. R. et al., 2011 (18 countries)	Gardasil (2,020 males)	225 or 450 ug of AAHS (2,029 males)	14.1% of subjects and 14.6% of controls had a systemic adverse event within 15 days
HPV – Cervarix (**GSK**)	None declared	Khatun S. et al., 2012 (Bangladesh)	Cervarix (50 girls)	Nothing given (17 girls)	Vomiting occurred in 8% of subjects after 1st dose, 10% after 2nd dose, and 32% after 3rd dose
HPV - Cervarix (**GSK**)	Funded by **GSK** and authors include **GSK** employees	Kim S. C. et al., 2011 (Korea)	Cervarix (149 women)	500 ug Aluminum Hydroxide (76 women)	"fatigue, myalgia and headache was frequent in both groups" and 22.8% of subjects and 13.2% of controls reported a medically significant adverse condition(s)
HPV - Gardasil (**Merck**)	Authors include **Merck** employees	Levin M. J. et al., 2010 (U.S.)	Gardasil (96 HIV positive children)	"identical placebo" (30 HIV positive children)	7% of subjects and controls had grade 3 or 4 event w/n 14 days, and 15 AEs were not graded
HPV - Gardasil (**Merck**)	Funded by **Merck** and authors include **Merck** employees	Li R. et al., 2012 (China)	Gardasil (302 people)	225 or 450 ug of AAHS (298 people)	42.7% of subjects and 39.9% of controls had systemic adverse event
HPV - Gardasil (**Merck**)	Funded by **Merck**	Kang, S. et al. 2008 (Korea)	Gardasil (117 females)	225 ug of AAHS (59 females)	31.6% of subjects and 44.1% of controls had systemic adverse reaction within 14 days
HPV - Gardasil (**Merck**)	Funded by **Merck** and authors include **Merck** employees	Clark, L.R. et al. 2013 (global)	Gardasil (373 women)	225 ug of AAHS (393 women)	49% of subjects and 41% of controls had systemic reactions, both had similar rate of SAEs

The above tables make clear that HHS is misleading the public when it labels these studies as "vaccinated versus unvaccinated" because the control group in each study almost always received another vaccine and/or an active ingredient found in the vaccine.[255]

Little comfort should be derived from the fact that the rate of serious adverse events is the same in an experimental vaccine test group and a control group receiving another vaccine or toxic substance, especially when that rate is higher than what would be expected in the general population. For example, it is troubling that a serious adverse event rate of over 30% (or even 2% of babies) is dismissed just because it occurred in both the subject and control groups, especially where the control group received another vaccine or toxic substance.

These outcomes of these purported "vaccinated versus unvaccinated" studies should be cause for concern regarding vaccine safety, not used as proof of safety.

Finally, it is evident that the real goal of HHS's "comprehensive review" was *not* about providing good scientific evidence to reassure the public that the vaccines on HHS's childhood vaccine schedule are safe. As the introduction to the review makes clear, it was about assuring high vaccine uptake, even at the expense of throwing away objectivity and basic scientific principles to produce a report that provides only the superficial appearance of vaccine safety for the public.[256] Indeed, the review begins by focusing upon and bemoaning that "vaccination rates remain well below established Healthy People 2020 targets for many vaccines" and that "Increasing vaccination rates remains critically important."[257] HHS even laments in its review that "public concerns about vaccine safety continue to persist" despite "the rigorous processes new vaccines must undergo before receiving approval" and that they meet "stringent criteria for safety."[258] HHS's predetermined objective and conclusion is thus made clear from the outset of its review.

Despite its predetermined conclusion regarding vaccine safety and the limitations placed on the inclusion of studies as discussed above, the 2014 review still found that vaccines can cause babies and children to develop numerous serious adverse reactions, such as febrile seizures, arthralgia (pain in the joints), thrombocytopenic purpura (the immune system attacking the body's own platelets), meningitis (inflammation of the membranes surrounding the brain and spinal cord), and encephalitis (inflammation of the brain).[259]

---

[255] As for the one purported "vaccinated versus unvaccinated" varicella (chicken pox) vaccine study, it compared a test group of 54 children with systemic lupus erythematosus that either received or did not receive varicella with a control group of 28 healthy children that received varicella. (Weinberg, A. et al. 2010 (U.S.).)

[256] https://www.ncbi.nlm.nih.gov/books/NBK230053/

[257] https://www.ncbi.nlm.nih.gov/books/NBK230053/

[258] https://www.ncbi.nlm.nih.gov/books/NBK230053/

[259] https://www.ncbi.nlm.nih.gov/books/NBK230053/

Given all of the foregoing issues with the 2014 review, it is not surprising that HHS's response letter only cites an executive summary of this review.[260] The full text of this review, which HHS understandably wanted to avoid publicizing as part of its response, is available at the URL in the footnote to this sentence.[261]

C. Studies Published After HHS's 2014 Review Reaffirm the Above Concerns

Apart from the 2014 review, HHS's response provides a link to the CDC website which HHS states contains a "list of CDC vaccine safety publications" which "address several of the vaccine-injury pairs that have been identified in the reports mentioned above."[262] These studies, however, add little to closing the gap regarding whether a causal relationship exists for the 173 vaccine-injury pairs from the 1994 and 2011 IOM Reports.

The studies published prior to August 2013 should have been swept up by HHS's 2014 "comprehensive review" (discussed above), which HHS asserts encompassed all vaccine safety studies prior to August 2013.[263] As for studies published after August 2013, those based on VAERS data cannot be used to determine causation for any vaccine-injury pair because according to HHS: "A major limitation of VAERS data is that VAERS cannot determine if the adverse health event reported was caused by the vaccination."[264] What remains are only 6 non-VAERS studies published after August 2013 on the CDC webpage cited by HHS which analyze any of the relevant vaccine-injury pairs from the 1994 and 2011 IOM reports.[265]

HHS's response to our letter sought to mislead the public into believing it has conducted studies to fill the vaccine safety science gaps identified by the IOM between 1991 and 2013, when this is clearly not the case. HHS's response and its 2014 "comprehensive

---

[260] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

[261] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf

[262] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

[263] https://www.ncbi.nlm.nih.gov/books/NBK230053/

[264] https://wonder.cdc.gov/vaers.html. HHS also explains that VAERS cannot be used "to determine causation" because "there is lack of an unvaccinated group for comparison in VAERS. https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html. Also, since VAERS is a passive reporting system, the absence of adverse event reports in VAERS cannot establish safety. https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf

[265] Five of these six studies were conducted using the VSD and the issues with the VSD are discussed below in Section IX; and the authors in half of these studies received funding from the pharmaceutical companies whose vaccines were being reviewed. The six studies are: (1) Hambridge (2014) - Reviewed risk of seizures, but expressly excluded all unvaccinated children and instead compared the rate of seizures within 2 days or between 7 to 10 days of vaccination (depending on vaccine) with the rate of seizures during the next 14 days plus the 14 days starting four weeks before vaccination. It found an increased risk of seizures from some vaccines. (2) Rowhani-Rahbar (2013) - Compared risk of seizures 7 to 10 days after vaccination with the risk in days 1 to 6 plus 11 to 42 after vaccination between MMRV alone or MMR and V concurrently but separately. (3) Klein (2015) - Also compared MMRV alone with MMR and V concurrently but separately. (4) McCarthy (2013) - Evaluated influenza vaccine, but excluded reactions on the day of vaccination for most conditions, had no unvaccinated control, and comingled data for children and adults with the exception of seizures. As for seizures, only included seizures occurring within one day of vaccination and excluded complex febrile seizures. (5) Kawai (2014) - Also reviewed influenza vaccine, had same issues as McCarthy, plus excluded all reactions occurring during outpatient visits when vaccines are administered. (6) Daley (2014) - Compared receipt of DTaP-IPV as single injection with receipt of DTaP and IPV at same time in separate injections and excluded most reactions during outpatient visits.

review" provide further evidence that it has failed to fulfill and cannot be trusted to fulfill its critical statutory vaccine safety duties.

Please respond to the above points with relevant studies, and please provide answers to the specific questions raised in Appendix A.

V. FAILURE TO IDENTIFY CHILDREN SUSCEPTIBLE TO VACCINE INJURY

In our opening letter we noted that the IOM in 1994 asserted that it "was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not" and hence urged that "research should be encouraged to elucidate the factors that put certain people at risk."[266] We also pointed out that in 2013, the IOM acknowledged this research still had not been conducted, stating that it

> found that evidence assessing outcomes in sub populations of children who may be potentially susceptible to adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited.[267]

We thereafter asked that HHS "advise when [it] intends to begin conducting research to identify which children are susceptible to serious vaccine injury" and "[i]f HHS believes it has commenced this research, please detail its activities regarding same."[268]

We appreciate that HHS's response appears to acknowledge that this is an important area of study by asserting that "HHS is currently supporting several initiatives that focus on advancing research" that would identify which children are susceptible to serious vaccine injury.[269] Unfortunately, the two sources HHS cites do not support that it is actually conducting this research.

HHS first cites the "About Us" page for the Human Immunology Project Consortium (**HIPC**).[270] To be sure, this webpage asserts that "the HIPC program will … establish predictors of vaccine safety in different populations."[271] But, none of the projects listed on the "HIPC Projects" webpage nor the 64 HIPC-funded studies within the associated

[266] https://www.nap.edu/read/2138/chapter/12#307. See also https://www.nap.edu/read/1815/chapter/9
[267] https://www.nap.edu/read/13563/chapter/9#130. See also https://www.nap.edu/read/13164/chapter/5#82
[268] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[269] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[270] https://www.immuneprofiling.org/hipc/page/showPage?pg=sci-about
[271] https://www.immuneprofiling.org/hipc/page/showPage?pg=sci-about

ImmuneSpace database are aimed at establishing the predictors of susceptibility to vaccine injury in the general United States pediatric population.[272]

While HIPC has studiously avoided supporting projects that could identify which children should not receive one or more vaccines due to increased risk of vaccine injury, it has supported projects aimed at identifying biomarkers of inter-subject variability in vaccine immunogenicity (*i.e.*, the ability of recipients to produce a better immune response to a currently licensed vaccine, such as the Hepatitis B vaccine), even though similar tools could be utilized to search for predictors of increased risk of injury from those same vaccines.[273] The ImmuneSpace database even contains studies intended to *expand* the use of vaccines in subgroups where those vaccines are currently contraindicated for use.[274] Thus, HHS's assertion that the HIPC program is conducting studies to identify which children are susceptible to vaccine injury was incorrect.

The second source HHS cites does not fare much better.[275] It provides a list of the five vaccine safety studies HHS has directly funded since 2015, two of which relate to identifying which children would be injured by a vaccine.[276] The first "aims to identify inherited, immunologic, and clinical factors that may predict the occurrence of febrile seizures after measles vaccination" and the second "aims to analyze the genetic determinants of the immune response following yellow fever vaccination among individuals who experience serious adverse events."[277]

Funding only two studies in three years aimed at assessing which children are likely to be vaccine injured is far too slow a pace.[278] There are also serious issues with these studies.

The principal investigator for the measles vaccine febrile seizure study, Dr. Nicole P. Klein, received $1,706,230.28 in funding from the manufacturer of the measles vaccine, Merck, between 2015 and 2017.[279] Selecting someone who receives millions of dollars in funding from Merck to conduct a study about the safety of a Merck vaccine raises serious concern about the study author's objectivity. If Dr. Klein were to produce and publish findings that were adverse to Merck's interests, she may place her future funding from Merck in jeopardy. This conflict should have been obvious to HHS prior to selecting Dr. Klein to conduct this study.

---

[272] https://www.immuneprofiling.org/hipc/page/showPage?pg=projects; https://www.immunespace.org/

[273] https://www.immuneprofiling.org/hipc/page/showPage?pg=projects

[274] For example, a live varicella vaccine, which is currently contraindicated per the CDC's guidelines for immunocompromised children, is being studied in renal transplant recipients. ImmuneSpace project SDY357, *VZV Evaluation of the Safety and Immunogenicity of Varivax (Live-Attenuated Varicella-Zoster Virus Vaccine) in Pediatric Renal Transplant Recipients*.

[275] https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

[276] https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

[277] https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

[278] https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

[279] https://openpaymentsdata.cms.gov/physician/1081946/payment-information

As for the yellow fever study, that vaccine is *not* a routine childhood vaccine in the U.S. and the resources for this study – especially when only two studies are being funded in three years – would have been far better spent assessing biomarkers for predicting which children are at increased risk of suffering injuries from childhood vaccines routinely used in the United States. For example, HHS could have financed studies seeking to identify bio-markers that would predict which children are likely to experience one or more of the following serious injuries that HHS concedes are caused by one or more routinely administered childhood vaccines: brachial neuritis, encephalopathy, encephalitis, chronic arthritis, thrombocytopenia, and Guillain- Barré syndrome.[280]

Between 2015 and 2017, HHS spent over $14 billion purchasing and promoting the universal use of HHS recommended vaccines.[281] During this same time period, HHS certainly could and should have funded more than two studies seeking to identify which children should be excluded from receiving one or more vaccines in order to prevent a serious vaccine injury.[282] This research should also not be conducted by individuals who receive funding from the pharmaceutical company whose vaccine product is being reviewed.

VI. UNSUPPORTED CLAIM THAT "VACCINES DO NOT CAUSE AUTISM"

HHS declares on its website that "Vaccines Do Not Cause Autism."[283] Our letter therefore asked for the studies that HHS relies upon to make this claim.[284] HHS's response, however, fails to provide a single study to support its claim that *none* of the vaccines given to children by one year of age cause autism.[285] HHS's 2014 "comprehensive review" of vaccine safety even expressly stated it could not identify a single study to support that DTaP or Hepatitis B vaccines do not cause autism.[286] HHS nonetheless continues to contend that "vaccines do not cause autism" when its own "comprehensive review" concedes it cannot scientifically support this claim.

This section will first review the points made in our opening letter regarding vaccines and autism which HHS failed to address and then go through each of the five citations HHS provides to support its claim that "vaccines do not cause autism."

---

[280] https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf
[281] https://www.hhs.gov/sites/default/files/fy2017-budget-in-brief.pdf?language=es
[282] https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html
[283] https://www.cdc.gov/vaccinesafety/concerns/autism.html; https://www.hhs.gov/programs/topic-sites/autism/index.html
[284] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[285] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[286] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf

A. Vaccines-Autism Points from Opening Letter Unrebutted by HHS

As explained in our opening letter, HHS paid the IOM to conduct a review regarding whether, among other things, there is a causal relationship between autism and the DTaP vaccine.[287] In 2011, the IOM published its review and stated it could not locate a single study supporting that DTaP vaccine does not cause autism.[288] The IOM therefore concluded:

> The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism.[289]

In fact, the only study the IOM could locate regarding whether DTaP vaccine causes autism concluded there *was* an association between DTaP and autism.[290]

Our opening letter further asserted that, like the DTaP vaccine, there are also no published studies showing that autism is not caused by vaccines for Hepatitis B, Rotavirus, Hib, Pneumococcal, Polio, Influenza, Varicella, or Hepatitis A – each of which HHS's vaccine schedule recommends babies receive, typically multiple times, by six months of age.[291] HHS's response fails to provide a single study to rebut the foregoing.

We further asserted that HHS has failed to address the science that does support a link between vaccines and autism.[292] We gave the example that HHS has not addressed a study which found a 300% increased rate of autism among newborns receiving the Hepatitis B vaccine at birth compared to those that did not.[293] Nor did HHS address two pilot studies recently published out of the School of Public Health at Jackson State University which showed vaccinated children had a 420% increased rate of autism compared to unvaccinated children, and vaccinated preterm babies had an even higher rate.[294] We also pointed out that there is a compelling body of science that supports a clear connection between aluminum adjuvants in vaccines and autism, even citing a complete write-up summarizing the studies supporting same.[295] Yet, HHS failed to directly or substantively address any of the foregoing.

---

[287] https://www.nap.edu/read/13164/chapter/2#2
[288] https://www.nap.edu/read/13164/chapter/12#545
[289] https://www.nap.edu/read/13164/chapter/12#545
[290] https://www.nap.edu/read/13164/chapter/12#545 (Ironically, this study was discarded "because it provided data from a passive surveillance system [VAERS] and lacked an unvaccinated comparison population," which is true of much of HHS's "safety science.")
[291] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent. html
[292] https://www.cdc.gov/vaccinesafety/concerns/autism.html
[293] http://hisunim.org.il/images/documents/scientific_literature/Gallagher_Goodman_HepB_2010.pdf
[294] http://www.oatext.com/pdf/JTS-3-186.pdf; http://www.oatext.com/pdf/JTS-3-187.pdf
[295] http://vaccine-safety.s3.amazonaws.com/WhitePaper-AlumAdjuvantAutism.pdf

Moreover, we asserted that HHS's claim that "Vaccines Do Not Cause Autism" improperly relies almost exclusively upon studies examining only one vaccine, MMR (administered no earlier than one year of age), or only one vaccine ingredient, thimerosal.[296] HHS's response, however, did not explain why studies that exclusively evaluated one vaccine or only one vaccine ingredient, while ignoring the balance of HHS's childhood vaccine schedule, support HHS's sweeping declaration that "Vaccines Do Not Cause Autism."

As for the one vaccine HHS claims it has studied with regard to autism, MMR, we pointed out that Senior CDC Scientist, Dr. William Thompson[297], has provided a statement through his attorney that HHS "omitted statistically significant information" showing an association between the MMR vaccine and autism in the first and only MMR-autism study ever conducted by HHS with American children.[298] Dr. Thompson, in a recorded phone call, stated the following regarding concealing this association: "Oh my God, I can't believe we did what we did. But we did. It's all there. It's all there. I have handwritten notes."[299] Dr. Thompson further stated on that call:

> I have great shame now when I meet families with kids with autism because I have been part of the problem … the CDC is so paralyzed right now by anything related to autism. They're not doing what they should be doing because they're afraid to look for things that might be associated. So anyway there's still a lot of shame with that. … I am completely ashamed of what I did.[300]

Hence, as for MMR, the only vaccine actually studied by HHS with regard to autism, it appears HHS may have concealed an association between that vaccine and autism.[301] HHS's letter completely ignores this serious allegation by one of its own senior scientists.

B. HHS's Citations Do Not Support that Vaccines Do Not Cause Autism

Instead, HHS's response merely provides five links in response to our request for the studies supporting that pediatric vaccines do not cause autism. The content of these five links all directly reinforce and confirm the very concerns raised in our opening letter.

---

[296] https://www.cdc.gov/vaccinesafety/concerns/autism.html

[297] Dr. Thompson has been a scientist at CDC for nearly two generations and a senior scientist on over a dozen CDC publications at the core of many of its vaccine safety claims. https://www.ncbi.nlm.nih.gov/pubmed

[298] http://www.rescuepost.com/files/william-thompson-statement-27-august-2014-3.pdf

[299] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio

[300] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio

[301] Studies of MMR and autism are also erroneous because of healthy user bias, which has been emphasized as a serious source of error in epidemiological vaccine safety studies by CDC scientists. https://doi.org/10.1093/oxfordjournals.aje.a116479

The *first* link is to a document entitled "Science Summary: CDC Studies on Thimerosal in Vaccines."[302] The studies in this document are plainly insufficient to support the claim that "vaccines do not cause autism" as they at best only address whether thimerosal causes autism.

The *second* link is to an IOM report from 2004 entitled "Immunization Safety Review: Vaccines and Autism."[303] This report also cannot support the CDC's claim about all vaccines because it *only* addresses the MMR vaccine and thimerosal with regard to autism. It is nonetheless noteworthy that this report was issued before the admission by Dr. Thompson that the CDC concealed an association between the MMR vaccine and autism, and it is further noteworthy that even this review stated that the IOM "committee's conclusion did not exclude the possibility that MMR could contribute to autism in a small number of children" and that "models for an association between MMR and autism were not … disproved."[304] But, again, this report is plainly insufficient to support the claim that "vaccines do not cause autism," as it at best only addresses whether the MMR vaccine and thimerosal cause autism.

The *third* link is a study which only looks at one vaccine component – antigens – comparing '*vaccinated* children' with '*vaccinated* children' with different antigen exposure.[305] This study again says nothing about whether any particular vaccine or HHS's childhood vaccine schedule causes autism. This study even concedes: "ASD with regression, in which children usually lose developmental skills during the second year of life, *could* be related to exposure in infancy, *including vaccines*."[306]

This antigen exposure study could have compared children receiving no-antigens, meaning no vaccines, with children receiving vaccine antigens. That would finally provide real data. Instead, the study engages in yet another nonsensical whitewash review in which it compares vaccinated children with vaccinated children, with the only real difference typically being that some children received DTaP while others received DTP.[307] All vaccines on the CDC childhood schedule, including DTaP, have been estimated to have between 1 and 69 antigens per dose while the DTP vaccine, no longer used in the U.S., is estimated to have 3,002 antigens per dose.[308] Hence, to compare antigen exposure, this study simply looks at one group of almost entirely fully vaccinated children who received DTaP with another group of almost entirely fully vaccinated children who received DTP.

---

[302] https://www.cdc.gov/vaccinesafety/pdf/cdcstudiesonvaccinesandautism.pdf
[303] http://nationalacademies.org/hmd/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
[304] http://nationalacademies.org/hmd/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
[305] https://www.ncbi.nlm.nih.gov/pubmed/23545349
[306] https://www.ncbi.nlm.nih.gov/pubmed/23545349 (emphasis added)
[307] https://www.ncbi.nlm.nih.gov/pubmed/23545349
[308] https://www.ncbi.nlm.nih.gov/pubmed/23545349

This study further admits the manner in which it counted "antigens" is not a valid measure of the actual immunogenicity of any given vaccine:

> Admittedly, this approach assumes that all proteins and polysaccharides in a vaccine evoke equivalent immune responses, whereas some proteins actually may be more likely than others to stimulate an immune response. Moreover, the calculations do not take into account the number of epitopes per antigen or the immunologic strength of each epitope. [309]

In addition, HHS's antigen study only included children vaccinated in the late 1990s, despite being published in 2013, by which time the following additional vaccines had already been added to HHS's childhood vaccine schedule: PCV13, Influenza, Hepatitis A, Meningococcal, Tdap, and HPV.[310]

This study further ignores the fact that while "antigens" (as defined in the study) in vaccines have decreased since the late 1990s, the amount of aluminum adjuvant, a neuro-and-cyto-toxic immune stimulant, used in vaccines has significantly *increased*. Indeed, in 1983 there was one aluminum-adjuvanted vaccine on HHS's vaccine schedule, in 1998 there were three (Hep B, DTaP, Hib[311]), and by 2018 the vaccine schedule included the following aluminum-adjuvanted vaccines: (1) Hep B, (2) DTaP, (3) Hib[312], (4) PCV13, (5) Hep A, (6) Tdap, and (7) HPV (and newer vaccines contain large amounts of aluminum adjuvant).[313] Also, the amount of aluminum adjuvant from Hep B, DTaP and Hib vaccines has increased since the late 1990s.[314] For example, the product with the lowest amount of aluminum for DTaP (DTP) had approximately half the amount of aluminum in 1998 as it did in 2018, and the percent of children receiving these three vaccines has increased markedly since the 1990s.[315] The antigen study HHS cites not only ignores the increasing amount of aluminum adjuvant included in childhood vaccines since 1999, it studiously ignores (as discussed below) the compelling body of science implicating this rising amount of aluminum adjuvant in vaccines with causing neurological dysfunction and autism.[316]

But even putting all these limitations aside, this antigen study says nothing about whether any particular vaccine or group of vaccines cause autism, and, at best, relates to the

---

[309] https://www.ncbi.nlm.nih.gov/pubmed/23545349

[310] https://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a2.htm; https://www.ncbi.nlm.nih.gov/pubmed/23545349 (This study also excluded children with fragile X syndrome, and thus cannot address if vaccinating children with fragile X can cause autism.)

[311] In 1998, 1 out of 4 licensed Hib vaccines contained aluminum. Physicians' Desk Reference, 1998, http://www.pdr.net

[312] In 2018, 1 out of 3 licensed Hib vaccines contained aluminum. Physicians' Desk Reference, 2018, http://www.pdr.net

[313] https://www.cdc.gov/vaccines/schedules/images/schedule1983s.jpg; https://www.cdc.gov/mmwr/preview/mmwrhtml/00056261.htm; https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

[314] Compare 1998 and 2018 editions of the Physicians' Desk Reference. http://www.pdr.net

[315] Ibid.; https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/data-reports/index.html

[316] http://vaccine-safety.s3.amazonaws.com/WhitePaper-AlumAdjuvantAutism.pdf

potential connection between antigen exposure and autism (albeit in a study that, in its best light, is unreliable).

The *fourth* link HHS cites is the very IOM review from 2011 cited in our opening letter.[317] However, as we noted in our letter, the IOM could not identify a single study which supports the claim that DTaP does not cause autism.[318] Even more astonishing, a different part of HHS's response letter cites the 2014 "comprehensive review" which again could not identify a single study to support the claim that DTaP does not cause autism.[319]

HHS's 2014 review also searched for studies that would support the claim that the Hepatitis B vaccine does not cause autism and also did not find a single study to support this claim.[320] In fact, even after using its strict selection criteria to toss 99% of all studies out of its review, it nevertheless resulted in the inclusion of a vaccine-autism study that was *not* funded by a pharmaceutical company reviewing its own vaccine.[321] This study, from the Stony Brook University Medical Center, found a 300% increased rate of autism among newborns receiving the Hepatitis B vaccine at birth compared to those who did not get this vaccine at birth.[322] The 2014 review summarizes the results of this study as follows:

> Result was significant for the risk of autism in children who received their first dose of Hepatitis B vaccine during the first month of life (OR 3.00, 95% CI 1.11, 8.13), compared with those who received the vaccination after the first month of life or not at all.[323]

Having found one study that showed an association, and no studies to disprove this association, HHS's review did not claim that the Hepatitis B vaccine does not cause autism.[324] Rather, it concluded it does not know whether the Hepatitis B vaccine causes autism.[325] In short, the fourth link cited by HHS in fact proves, once again, that HHS cannot claim that vaccines do not cause autism.

The *fifth* (and final) link HHS cites in its letter is the "Strategic Plan for Autism Spectrum Disorder Research" by the Interagency Autism Coordinating Committee, which is part of HHS.[326] Remarkably, this 196 page strategic plan outlines dozens of research

[317] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[318] http://nationalacademies.org/HMD/Reports/2011/adverse-effects-of-vaccines-evidence-and-causality.aspx
[319] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[320] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[321] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[322] http://hisunim.org.il/images/documents/scientific_literature/Gallagher_Goodman_HepB_2010.pdf
[323] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[324] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[325] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[326] https://iacc.hhs.gov/publications/strategic-plan/2017/strategic_plan_2017.pdf

priorities, but does not once mention closing the vaccine safety science gap regarding whether DTaP, Hepatitis B, and every other vaccine given by one year of age cause autism.[327]

The strategy plan even explains that "neuroinflammation" may cause autism, but ignores the fact that neuroinflammation (a.k.a., encephalitis or encephalopathy) is a known reaction to numerous vaccines. For example, encephalitis or encephalopathy are listed as adverse reactions in the package inserts for the following vaccines injected multiple times into babies during their first few months of life: DTaP (Infanrix, Daptacel), Hepatitis B (Recombivax-HB, Engerix -B) and combination vaccines (Pediarix, Pentacel).[328] The strategic plan also recognizes "immune dysregulation" – which again can be caused by vaccines – may cause autism.[329] It also explains that current science suggests "that ASD results from subtle alterations during brain development [including during the first year of life] that affect brain structure, function and connectivity," which have been demonstrated to occur in lab animals following injection of comparable amounts of pediatric vaccines and/or aluminum adjuvants used in pediatric vaccines.[330]

This strategic plan even outlines numerous large scale studies looking at a plethora of environmental exposures, but apparently none of these include looking at the exposure to vaccines.[331] This is despite the fact that numerous peer-reviewed studies have found that, when surveyed, between 40% and 70% of autism parents squarely blame vaccines for their child's autism.[332] It would be simple to review vaccine exposures along with the hundreds of other exposures already being reviewed in these studies, but for apparently political reasons, HHS has chosen not to address this issue.

C. Vaccine-Autism Concerns Always Broader than MMR and Thimerosal

HHS directs all conversation regarding vaccines and autism toward MMR and thimerosal, despite longstanding concerns regarding the connection between autism and other vaccines and other vaccine ingredients.[333] For example, the concern that pertussis containing vaccines could cause immune and brain dysfunction, including autism, was identified as a research priority in the 1986 Act. Indeed, Congress, when passing the Act,

---

[327] https://iacc.hhs.gov/publications/strategic-plan/2017/strategic_plan_2017.pdf

[328] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm124514.pdf; https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm103037.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM241874.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109810.pdf

[329] https://onlinelibrary.wiley.com/doi/book/10.1002/9781118663721

[330] https://iacc.hhs.gov/publications/strategic-plan/2017/strategic_plan_2017.pdf; http://vaccine-safety.s3.amazonaws.com/WhitePaper-AlumAdjuvantAutism.pdf

[331] https://iacc.hhs.gov/publications/strategic-plan/2017/strategic_plan_2017.pdf

[332] https://www.ncbi.nlm.nih.gov/pubmed/16685182; https://www.ncbi.nlm.nih.gov/pubmed/25398603; https://www.ncbi.nlm.nih.gov/pubmed/16547798; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1448378/

[333] https://www.gpo.gov/fdsys/pkg/STATUTE-100/pdf/STATUTE-100-Pg3743.pdf

directed HHS to review the scientific evidence for whether pertussis containing vaccines can cause, among other conditions, autism.[334] As expressly provided in the 1986 Act:

> Health and Human Services shall complete a review of all relevant medical and scientific information … on the nature, circumstances, and extent of the relationship, if any, between vaccines containing pertussis … and … Autism[335]

Implementing the foregoing congressional directive, HHS commissioned the IOM in 1989 to identify any and all medical and scientific literature addressing whether pertussis-containing vaccines can cause autism.[336] The IOM conducted this review and issued its report in 1991.[337] While the IOM found at least some evidence bearing on causation for the 20 conditions other than autism it reviewed, the IOM could not find a single shred of evidence to support the claim that pertussis containing vaccines do not cause autism.[338] This is because no studies had been conducted to determine whether pertussis-containing vaccine cause autism. This is part of why the IOM's report in 1991 said:

> In the course of its review, the committee found many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. … If research capacity and accomplishment in this field are not improved, future reviews of vaccine safety will be similarly handicapped.[339]

Yet when HHS commissioned the IOM twenty-two years later to assess the evidence bearing on whether pertussis containing vaccines cause autism – as this remained (per HHS) one of the most commonly claimed injuries from this vaccine – the IOM again in 2011 had the same conclusion:

> The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism.[340]

HHS itself reached this same conclusion again in its 2014 "comprehensive review."[341] These reports show clearly that HHS has known for 27 years that it does not have the scientific

---

[334] https://www.gpo.gov/fdsys/pkg/STATUTE-100/pdf/STATUTE-100-Pg3743.pdf
[335] https://www.gpo.gov/fdsys/pkg/STATUTE-100/pdf/STATUTE-100-Pg3743.pdf
[336] https://www.nap.edu/read/1815/chapter/1#v
[337] https://www.nap.edu/read/1815/chapter/1
[338] https://www.nap.edu/read/1815/chapter/2#7
[339] https://www.nap.edu/read/1815/chapter/9
[340] https://www.nap.edu/read/13164/chapter/12?term=autism#545
[341] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf

studies to support its claim that "vaccines do not cause autism," and has willfully chosen to remain ignorant rather than test its *a priori* assumption that vaccines do not cause autism.[342]

D. HHS's Refusal to Study Vaccines-Autism Connection is Troubling

HHS has even remained silent and refused to seriously study the vaccine-autism connection despite the fact that HHS's leading autism expert, Dr. Andrew Zimmerman – an expert whom HHS relied upon in the *Cedillo v. HHS* case in Vaccine Court to claim that vaccines never cause autism – has changed his expert opinion.[343]

Dr. Zimmerman is a former Director of Medical Research at the Center for Autism and Related Disorders at the Kennedy Krieger Institute and Johns Hopkins University School of Medicine, and is regarded as the leading national authority on autism and mitochondrial disorder.[344] Dr. Zimmerman testified on November 9, 2016 that vaccines can in fact cause autism and even answered "Yes" when asked under oath: "Do other people in your field, reputable physicians in your field, hold the opinion that vaccines can cause the type of inflammatory response that can lead to a regressive autism?"[345] Dr. Zimmerman further testified that once HHS understands and accepts the causal relationship between vaccines and autism, "it will prevent the development of autism in quite a few children."[346]

Dr. Zimmerman's similarly credentialed colleague, Dr. Richard Kelley, also provided the following very revealing testimony in a deposition under oath:

> *Lawyer: Do you agree with the statement that vaccines do not cause autism?*
>
> Dr. Kelley: No
>
> *Lawyer: Is it generally accepted in the medical community that vaccines do not cause autism?*
>
> Dr. Kelley: It is a common opinion.
>
> *Lawyer: It is generally accepted in the medical field that vaccines do not cause autism?*
>
> Dr. Kelley: I have no basis to judge that. It is most often when physicians are commenting on that they say there is no proven association.
>
> *Lawyer: Do you know the position of the American Academy of Pediatrics about any link between vaccines and autism?*

[342] https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[343] https://childrenshealthdefense.org/child-health-topics/righting-wrongs/request-for-office-of-inspector-general-to-investigate-fraud-and-obstruction-of-justice/#_ftnref1
[344] https://books.google.com/books?isbn=1603588256
[345] https://books.google.com/books?isbn=1603588256
[346] https://books.google.com/books?isbn=1603588256

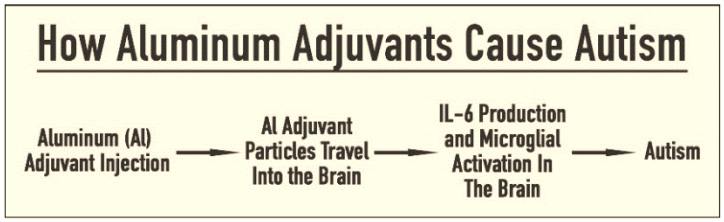
> Dr. Kelley: Yes. They also say there is no proven association.
>
> *Lawyer: Do you agree with the position of the American Academy of Pediatrics?*
>
> Dr. Kelley: I agree with their position as a public health measure. I don't agree with it scientifically.
>
> *Lawyer: You are actually arguing for a link between vaccines and autism in this case, aren't you?*
>
> Dr. Kelley: I am.
>
> *Lawyer: And that is contrary to the medical literature, isn't it?*
>
> Dr. Kelley: It's not contrary to the medical literature that I read. It is contrary to certain published articles by very authoritative groups who say there is no proven association in large cohort studies.
>
> *Lawyer: Your opinion is contrary to, say, the opinion of the CDC, correct?*
>
> Dr. Kelley: It is contrary to their conclusion. It is not contrary to their data.[347]

The view apparently held by HHS that "public health" demands hiding any relationship between vaccines and autism to assure high vaccine uptake, is troubling. This view (i) ignores the fact that the real "public health" emergency in the United States is that 1 in 36 children are now diagnosed with autism[348], (ii) stifles research into the association between vaccines on HHS's childhood vaccine schedule and autism, and (iii) forces HHS to ignore any science that does support a vaccine-autism connection.

Indeed, HHS appears frozen when confronted with replicated peer-reviewed studies, many of which were funded by HHS, regarding immune activation and aluminum adjuvants that support a causal relationship between the receipt of vaccines continuing aluminum adjuvants and the development of autism in children.[349] Our opening letter attached letters to HHS from world-renowned experts on the toxicity of aluminum adjuvants, each of whom strongly supported the contention that aluminum adjuvants may have a role in the etiology of autism and cited the body of science that supports their assertion.[350] This science reflects that: injected aluminum adjuvant is taken-up by immune cells (macrophages) at the injection site; these aluminum-adjuvant-loaded immune cells then travel through the lymph vessels to, among other places, the brain; the immune cells then unload their aluminum adjuvant cargo in the brain; and aluminum adjuvant in the

[347] https://books.google.com/books?isbn=1603588256
[348] https://www.cdc.gov/nchs/data/databriefs/db291.pdf
[349] http://icandecide.org/white-papers/ICAN-AluminumAdjuvant-Autism.pdf
[350] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf

brain causes a release of interleukin IL-6 and microglial activation, leading to autism.[351] Depicted in simple terms:



Despite years of vaccine safety advocacy demanding that HHS rebut, or at least address, the clear connection between aluminum adjuvant containing vaccines and autism, HHS appears unable to muster anything more than the public relations slogan – "Vaccines Do Not Cause Autism."

On May 24, 2014, Dr. Thompson explained that the CDC is "paralyzed right now by anything related to autism … because they're afraid to look for things that might be associated."[352] The reason for this fear may be that HHS has conceded or has been required by the Vaccine Court to pay financial compensation to at least a few dozen children where receipt of a vaccine on HHS's childhood vaccine schedule resulted in brain, neurological and/or immune dysfunction diagnosed as autism.[353] The damage awards in some of these cases were in the millions of dollars.[354] If a single study conducted by HHS shows that even 1 in 5 cases of autism are caused, directly or indirectly, by vaccines, it would result in approximately $1.3 trillion in liability.[355] Putting such potential liability into perspective, the entire federal budget in 2017 was $3.3 trillion.[356] This and the decimation of HHS's reputation if it were found that certain vaccines cause a significant fraction of autism cases, provide powerful incentives for HHS to *not* fund the basic scientific research needed to determine whether HHS's childhood vaccine schedule is a cause of autism.

It is hard to imagine that HHS has not already internally used the databases at its disposal, such as VSD, to compare the autism rate between vaccinated and unvaccinated children. If the results showed no difference in the autism rates between these two groups of children, no doubt this study would have been published. The fact that it has not been published is very concerning. For example, HHS recently published a study using the VSD which compared vaccination rates between autistic and non-autistic children, but only looked at vaccination rates *after* an autism diagnosis.[357] It is hard to imagine that HHS also

[351] http://icandecide.org/white-papers/ICAN-AluminumAdjuvant-Autism.pdf
[352] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio
[353] https://digitalcommons.pace.edu/cgi/viewcontent.cgi?article=1681&context=pelr
[354] https://digitalcommons.pace.edu/cgi/viewcontent.cgi?article=1681&context=pelr
[355] Since approximately 3.5 million American children have autism spectrum disorder and the approximate life time cost per individual is $1.9 million, total cost of care for just 20% of these individual is $1.3 trillion. www.autism-society.org/what-is/facts-and-statistics/
[356] https://www.cbo.gov/publication/53624
[357] https://www.ncbi.nlm.nih.gov/pubmed/29582071; https://www.cnn.com/2018/03/26/health/vaccination-rates-children-autism-study/index.html (lead author even concedes they "did not look at vaccination rates before the children were diagnosed with autism")

did not internally review the vaccination rate *before* the autism diagnoses. Of course, if this comparison showed that fewer vaccines resulted in less autism, publishing such a result would call into serious doubt the competence of HHS in ensuring the safety of vaccines and its childhood vaccine schedule, as well as involve trillions of dollars in financial liability for the harm caused.

HHS's approach to this issue ignores the tens of thousands of families across this country that have attested – often in videos available online – that their best judgment based on the totality of their parental experience with their child is that vaccination caused their child's autism. Numerous peer-reviewed studies have found that, when surveyed, between 40% and 70% of autism parents squarely blame vaccines for their child's autism.[358] Many of these surveys explain how parents express a clear personal experience with vaccination affirming this conclusion.[359]

The Vaccine Information Statement (**VIS**) produced by HHS for every vaccine, including for DTaP, provides that other relevant information regarding the vaccine is available at the CDC website, www.cdc.gov, which in turn claims that "Vaccines Do Not Cause Autism."[360] Because HHS has chosen to incorporate the CDC's website into the VIS as a resource, the information on that website regarding the relevant vaccine must, under federal law, be "based on available data and information."[361] But, based on available data and information, as discussed above, HHS cannot scientifically claim that "Vaccines Do Not Cause Autism." HHS must therefore remove this claim from the CDC website until it can produce the studies to support the claim that vaccines do not cause autism.

VII. HHS REFUSAL TO CONDUCT VACCINATED V. UNVACCINATED STUDY

In our letter, we asked that HHS advise whether it will "conduct adequately powered and controlled prospective as well as retrospective studies comparing total health outcomes of fully/partially vaccinated with completely unvaccinated children?"[362] HHS has failed to actually respond to this question.

A. IOM 2013 Review Highlights Need for Vaccinated v. Unvaccinated Study

HHS's response letter first cites the very same 2013 report by the IOM which we cited in our opening.[363] We cited this report because it clearly supports the need for a properly

[358] https://www.ncbi.nlm.nih.gov/pubmed/16685182; https://www.ncbi.nlm.nih.gov/pubmed/25398603; https://www.ncbi.nlm.nih.gov/pubmed/16547798; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1448378/

[359] https://www.ncbi.nlm.nih.gov/pubmed/16685182; https://www.ncbi.nlm.nih.gov/pubmed/25398603; https://www.ncbi.nlm.nih.gov/pubmed/16547798; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1448378/

[360] https://www.cdc.gov/vaccines/hcp/vis/current-vis.html; https://www.cdc.gov/vaccinesafety/concerns/autism.html

[361] 42 U.S.C. § 300aa-26

[362] Compare http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf with http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

[363] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

powered and controlled prospective study evaluating the health outcomes between vaccinated vs. unvaccinated children.[364] Indeed, HHS commissioned this review to assess the safety of HHS's early childhood vaccine schedule and hence, as explained by the IOM, its "literature searches and review were intended to identify health outcomes associated with some aspect of the childhood immunization schedule."[365] "Allergy and asthma, autoimmunity, autism, other neurodevelopmental disorders (e.g., learning disabilities, tics, behavioral disorders, and intellectual disability), seizures, and epilepsy were included as search terms."[366]

However, instead of answers, the IOM found that no studies had ever been conducted which compared the health outcomes of children receiving HHS's childhood vaccine schedule with children that had not been vaccinated:

> [F]ew studies have comprehensively assessed the association between the entire immunization schedule or variations in the overall schedule and categories of health outcomes, and no study … compared the differences in health outcomes … between entirely unimmunized populations of children and fully immunized children. Experts who addressed the committee pointed not to a body of evidence that had been overlooked but rather to the fact that existing research has not been designed to test the entire immunization schedule. …
>
> [Also,] studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted.[367]

Even when the IOM committee expanded its search for any evidence that could help it assess the safety of HHS's childhood vaccine schedule, it stated that it "found a paucity of information, scientific or otherwise, that addressed the risk of adverse events in association with the complete recommended immunization schedule."[368]

Due to the lack of science regarding the safety of HHS's vaccine schedule, the best the IOM could do was conclude: "There is no evidence that the schedule is not safe."[369] Left unsaid, but equally true: **there is no evidence that the schedule is safe**. That HHS finds the IOM's conclusion acceptable is troubling and another clear dereliction of its vaccine safety

[364] https://www.nap.edu/read/13563/chapter/1
[365] https://www.nap.edu/read/13563/chapter/2#5
[366] https://www.nap.edu/read/13563/chapter/2#5
[367] https://www.nap.edu/read/13563/chapter/2#5
[368] https://www.nap.edu/read/13563/chapter/6?term=paucity#70
[369] https://www.nap.edu/read/13563/chapter/2#12

duties. Just because HHS refuses to conduct the scientific studies necessary to establish if there is harm does not mean that no harm exists.

Equally troubling is that despite acute adverse events such as persistent crying or extreme lethargy in recently vaccinated babies that can last for days, the IOM acknowledges that science does not yet even know "if there is a relationship between short-term adverse events following vaccination and long-term health issues."[370] Without properly-controlled prospective long-term studies it is not possible to know whether acute vaccine reactions, including the more serious ones like brain inflammation and encephalitis, are causing long-term neurological damage (that takes the form of, for example, increasingly common developmental delays and behavioral disorders).

It is therefore remarkable that HHS cites the IOM report from 2013 as support for *not* conducting a longer-term properly powered and controlled study that would finally compare all health outcomes in vaccinated and unvaccinated children.

B. HHS's Desperation to Avoid Any Valid Vaccinated v. Unvaccinated Study

Hiding behind a claim that it would be unethical to conduct such a study is also without merit. Putting aside that it is unethical for HHS to continue promoting its childhood vaccine schedule as proven safe when HHS lacks the scientific studies necessary to validate the safety of its childhood vaccine schedule, there are ways to "ethically" conduct a vaccinated versus unvaccinated study. As we pointed out in our opening letter, the very IOM report from 2013 asserts it "is possible to make this comparison [between vaccinated and unvaccinated children] through analyses of patient information contained in large databases such as VSD."[371]

In response, HHS has not published this study. Given the numerous studies HHS publishes each year using the VSD, it is difficult to imagine that if such a study showed no health differences or that vaccinated children were healthier than unvaccinated children, HHS would not have already published that study.

Tellingly, instead of using the VSD to publish the relatively simple study comparing health outcomes between vaccinated and unvaccinated children, HHS instead spent a tremendous amount of resources to publish a 64-page white paper regarding conducting such studies using the VSD.[372]

---

[370] https://www.nap.edu/read/13563/chapter/5#45
[371] https://www.nap.edu/read/13563/chapter/2#13
[372] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

This white paper, prominently cited by HHS in its response letter, acknowledges that many chronic disorders children are experiencing today in epidemic numbers are biologically plausible outcomes from exposure to HHS's pediatric vaccination schedule but have not yet been properly studied.[373] While we should be encouraged by such an open admission, the white paper is revealing regarding HHS's approach to vaccine safety.

i. White Paper Guided by Pharmaceutical Company Insiders

First, this white paper was guided by pharmaceutical company insiders. As the white paper authors explain:

> Guided by subject matter expert engagement, we outlined a 4 staged approach for identifying exposure groups of undervaccinated children, developed a list of 20 prioritized outcomes, and described various study designs and statistical methods that could be used to assess the safety of the schedule.[374]

The subject matter experts relied upon to draft the white paper had serious financial and other conflicts of interest. For example, the first subject matter expert listed is Dr. Stanley Plotkin.[375] Dr. Plotkin earned millions of dollars in employment, consulting, and royalties from Merck, GSK, Sanofi and Pfizer (which, combined, manufacture nearly every vaccine on HHS's childhood vaccine schedule) including serving on the boards of the following for-profit pharmaceutical companies involved in vaccine development (while working on the white paper): Dynavax Technologies, VBI Vaccines, Mymetics, Inovio Biomedical Corp, CureVacAG, SynVaccine, GeoVax Labs, GlycoVaxyn AG, Adjuvance Technologies, BioNet Asia, Adcombia Biosciences, and Hookipia Biotech.[376] Three of the four other subject matter experts involved in creating the white paper were similarly conflicted.[377]

---

[373] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

[374] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

[375] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

[376] https://openpaymentsdata.cms.gov/physician/510771/summary; http://www.vaxconsult.com/cv-page/; https://patents.google.com/patent/US6290968B1/en; https://www.royaltypharma.com/royalty-pharma-acquires-royalty-interest-in-rotateq-from-the-childrens-hospital-foundation-for-182-million; http://people.equilar.com/bio/stanley-plotkin-dynavax-technologies/salary/91882; https://www.vbivaccines.com/about/scientific-advisory-board/; https://globenewswire.com/news-release/2009/09/09/404297/172906/en/Mymetics-Corporation-Announces-the-Appointment-of-Dr-Stanley-Plotkin-as-Chairman-of-the-Scientific-Advisory-Board-and-Election-of-New-Members.html; https://www.acornmanagementpartners.com/news-events/client-news/post/1713/vaccine-pioneer-joins-inovio-biomedicals-scientific; http://www.curevac.com/company/scientific-advisory-board/; https://www.synvaccine.com/about2; https://finance.yahoo.com/news/geovax-reports-2017-first-quarter-130000205.html; http://www.bionity.com/en/news/107511/glycovaxyn-ag-appoints-dr-stanley-plotkin-to-supervisory-board.html; http://adjuvancetechnologies.com/management-team/; http://www.jkdaily.com/articles/2628/20160322/asian-biotech.htm; http://www.abcombibio.com/advisors; http://hookipabiotech.com

[377] Walter A. Orenstein: https://www.ncbi.nlm.nih.gov/pubmed/18589064; https://www.ncbi.nlm.nih.gov/pubmed/16533116. Edgar K. Marcuse: https://www.ncbi.nlm.nih.gov/pubmed/10432034. M. Alan Brookhart: https://www.ncbi.nlm.nih.gov/pubmed/28370957.

Despite the foregoing, the authors of the white paper state that the "White Paper study team had no conflicts of interest to declare."[378]

The subject matter experts even gathered for a closed-door meeting with HHS to craft the white paper in Atlanta, Georgia in February 2014. Yet, the HHS authors excluded parents and parent organizations concerned about vaccine safety, admitting that the white paper study team "did not engage any parents or parental groups throughout the process."[379]

Bias is evident in the first paragraph of the white paper. Instead of stating its goal is to assess the actual safety of the vaccine schedule, the authors assert that "Maintaining high vaccination coverage within the population is critical" and that the enemy of this goal is "concern about the safety of vaccines," and in particular "the safety of vaccines given to young children."[380]

HHS even falsely asserts, more than once, that the 2013 IOM report concluded that "the current U.S. immunization schedule was safe," when it actually concluded: "There is no evidence that the schedule is not safe."[381] Ironically, it is precisely because of the lack of evidence to support safety that the IOM "highlighted four research questions of highest priority," with the first being "how do child health outcomes compare between fully vaccinated and unvaccinated children."[382]

ii. White Paper Expertly Designed to Support Status Quo

HHS was thus forced into a corner by the very report it commissioned from IOM. It now had to answer "how do child health outcomes compare between fully vaccinated and unvaccinated children."[383] But, the HHS officials and pharmaceutical company representatives who created this white paper are plainly concerned about revealing the health outcome differences between vaccinated and unvaccinated children. The authors dissuade such a comparison and suggest study parameters that would, among other things, result in eliminating the healthiest nonvaccinated subjects from any study.

A vaccinated versus unvaccinated study to assess the safety of HHS's childhood vaccine schedule should be straightforward. Such a study should compare the incidence of all adverse health conditions (ICD-9/10 codes) in vaccinated and unvaccinated children.

---

[378] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[379] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[380] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf (The white paper also asserts that "new knowledge generated about adverse events" should be used by "policy makers when weighing all available evidence about the benefits and risks of vaccination," when it should have said that this knowledge should be used to reduce/eliminate the risk of any identified adverse reaction.)
[381] https://www.nap.edu/read/13563/chapter/2#12
[382] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[383] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

Instead, the white paper only puts forth a handful of carefully culled conditions. It does this by first limiting its list to conditions that HHS and the pharmaceutical industry have previously studied.[384] Meaning, their prior bias was already built into the white paper's initial limited list of only 75 conditions.[385]

The authors then discarded those health conditions they deemed lacked "biological and mechanistic plausibility" with vaccination.[386] A lack of available biological and mechanistic studies is one of the major problems the IOM has complained about for decades. Removing outcomes because available science was lacking defeated the purpose of the exercise. Even so, this winnowing process resulted in a list of 43 adverse outcomes admitted by the subject matter experts to be plausibly caused by HHS's childhood vaccine schedule – a surprising admission given HHS's assurance that vaccine safety had already been established.[387] These 43 outcomes included autism spectrum disorder, attention deficit disorder, and numerous other neurological and immunological disorders.[388] Despite finding that all 43 of these outcomes were "plausible to study relative to the childhood immunization schedule," this list was nonetheless winnowed down to 20 conditions.[389] For example, autism was removed based on the demonstrably untrue claim it had "been extensively studied relative to the vaccination schedule."[390]

A comparison of all conditions between vaccinated and fully unvaccinated children, as directed by the IOM, is what should be conducted. Among other reasons, as HHS should be aware, vaccination can cause a spectrum of unexpected adverse effects.

For example, a recent study out of the University of Hong Kong, Queen Mary Hospital, and Centre for Influenza Research compared children receiving the influenza vaccine with those receiving a saline injection in a prospective randomized double-blind study.[391] Both groups had a statistically similar rate of influenza, but the group receiving the influenza vaccine had a statistically significant 440% increase in the rate of non-influenza infections.[392] Thus, the influenza vaccine increased children's susceptibility to other respiratory viral infections.

As another example, Dr. Peter Aaby is renowned for studying and promoting vaccines in Africa and has published over 300 peer-reviewed articles and studies regarding

---

[384] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[385] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[386] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[387] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[388] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[389] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[390] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[391] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[392] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/

vaccination.[393] In 2017, he and co-authors published a study finding that infants were 10 times more likely to die by 6 months of age following their DTP vaccination than those that did not receive any vaccines during the first 6 months of life.[394] Children vaccinated with DTP were dying from causes never associated with this vaccine, such as respiratory infections, diarrhea, and malaria.[395] This indicated that while DTP's purpose is to reduce the incidence of diphtheria, tetanus, and pertussis, it actually increased mortality from other infections.[396] The study therefore concludes:

> All currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis.[397]

Perhaps most concerning is that the above study was based on data from the 1980s that had been collecting dust for over 30 years.[398] This begs the question: what other serious vaccine injuries and non-specific adverse effects are being missed by neglecting to conduct desperately needed vaccine safety science comparing vaccinated and unvaccinated children.

Consider that there are over 420 disorders listed on package inserts of vaccines routinely administered to babies and children – a large portion of which are immune and nervous system disorders – which are *only* listed there because its manufacturer has a basis to believe there is a causal relationship between the vaccine and the occurrence of the adverse event.[399] Federal law is clear that this list should include "*only* those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."[400] Nonetheless, the white paper guides researchers to ignore every adverse health condition that develops following vaccination other than the 20 hand-picked conditions culled by HHS and pharmaceutical company insiders.

iii. White Paper Guides Researchers to Exclude Unvaccinated Children

The white paper then – in contravention to the primary directive of the IOM to compare health outcomes between *vaccinated* with *unvaccinated* children – advocates for comparing *vaccinated* with *vaccinated* children.[401] It begins by arguing that "Comparing fully vaccinated children to totally unvaccinated children would likely be highly confounded"

---

[393] https://www.ncbi.nlm.nih.gov/pubmed/?term=PETER+AABY%5BAuthor+-+Full%5D
[394] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/
[395] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/
[396] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/
[397] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/
[398] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[399] 21 C.F.R. 201.57; https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm
[400] 21 C.F.R. 201.57
[401] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

and, in numerous ways, derides conducting such a comparison.[402] The white paper then guides researchers to compare the health outcomes between fully vaccinated children and partially vaccinated children (which are typically also almost fully vaccinated).[403] But this is precisely the comparison that would be "highly confounded" because children are often only partially vaccinated because parents who stop vaccinating their children (and hence have partially vaccinated children) often do so because of a negative health outcome following a previous vaccination.[404] HHS and authors of the white paper are aware of this bias. As the authors of the white paper admit:

> Parents may alter their intended immunization schedules for a child who experiences a negative health outcome, particularly if the outcome is perceived to be a result of a vaccine.[405]

This means that the partially vaccinated children in the VSD may be sicker than the fully vaccinated children precisely because of their prior vaccinations. It is therefore a comparison of vaccinated with partially vaccinated children that is actually "highly confounded," but yet precisely the type of comparison the white paper strongly recommends. Such a comparison is also nonsensical since it will not answer the outstanding scientific questions that urgently need to be answered regarding the safety of HHS's childhood vaccine schedule.

iv. White Paper Guides Researchers How to Obtain Desired Results

If, despite the above recommendation not to do so, a researcher does conduct a vaccinated versus unvaccinated study, the white paper guides the researcher to use certain "adjustments" to control the study's outcome.

First, the white paper suggests that researchers "exclude unvaccinated children who had fewer than four outpatient visits during the first two years of life."[406] The purported reason for this "adjustment" is to ensure that children in the VSD with no recorded vaccination are actually unvaccinated. But, this "adjustment" is unnecessary because, as the authors of the white paper admit, many VSD sites already link to their state's centralized electronic immunization information system which tracks the vaccination status of every child in the state.[407] (Moreover, the authors of the white paper also admit that a "medical record review" revealed that the vaccination status was accurate for 94% of children when

[402] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[403] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[404] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[405] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[406] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf (emphasis added)
[407] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

they had at least one V-code for vaccine refusal and that in the VSD, "1,898 (0.6%) [children] had no vaccines and at least one V-code for vaccine refusal."[408])

The transparent reason for excluding unvaccinated children who do not have at least four outpatient visits is to exclude most or all of the very healthy unvaccinated children from the study.

HHS learned the importance of excluding children without outpatient visits from its experience in a prior study in which it found "a positive association between Hib and Hep B vaccination and the incidence of asthma."[409] If this result stood, it could have meant both loss of reputation for HHS and trillions of dollars of financial liability. To eliminate the association between vaccination and asthma, HHS first excluded children without at least one outpatient visit.[410] But when the association remained, HHS then excluded children without "at least two outpatient visits."[411] The result was that the positive finding was no longer statistically significant and a loss of reputation and trillions of dollars in liability was avoided. The white paper therefore advised that researchers restrict "their study populations to children with a minimum amount of health care utilization," such as excluding "unvaccinated children who had fewer than four outpatient visits."[412] Employing this adjustment, a researcher can make almost any safety signal disappear.

In case the above is not sufficient to eliminate a vaccine safety signal, the authors of the white paper created another escape hatch. Vaccine researchers are advised to include another supposed non-vaccine-related condition in each study as a "control" outcome, and if the incidence rate of the control condition is different in vaccinated and unvaccinated children, the study can be considered confounded and discarded.[413] On the surface, this approach seems sensible. However, the control conditions that the authors of the white paper suggest, such as well-child visits, are clearly related to vaccination rates.

Unvaccinated children often do not regularly go to well-child doctor visits because the major reason for these visits is vaccination; in fact, when they do, one-fifth of pediatricians report dismissing these families from their practice for refusing or requesting to delay one or more vaccines.[414] Hence, this control condition will likely yield a different incidence rate between vaccinated and unvaccinated children, providing the researchers

[408] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[409] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[410] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[411] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[412] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[413] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf
[414] https://www.ncbi.nlm.nih.gov/pubmed/26527552

with a reason to discard the study.[415] The "controls" suggested by the authors of the white paper are an apparent "insurance" to permit researchers, if the other "adjustments" they suggest do not work, to discard any study that produces concerning results about adverse health outcomes between vaccinated and unvaccinated children.

In summary, the white paper promotes the use of inappropriate study designs that will result in highly compromised studies. The authors appear dedicated to finding a desired result rather than letting the data speak for itself. They do this by narrowing studies to 20 outcome conditions, emphasizing vaccinated vs. vaccinated studies, and claiming vaccinated vs. unvaccinated studies are "highly confounded" and hence, if conducted, require adjustments to exclude healthy unvaccinated children and otherwise a "control" that permits discarding any finding that does not affirm the safety of HHS's childhood schedule.

The results-oriented nature of the white paper makes sense when considering it originates from HHS's Immunization Safety Office, which assists in defeating vaccine injury claims in Vaccine Court. It is plainly conflicted from providing guidance regarding or conducting this or any other vaccine safety study. If HHS really cared about vaccine safety, federal health officials would be requiring and advocating for adherence to the gold standard in scientific research – double-blind long-term placebo-controlled studies during pre-licensure trials, and straightforward vaccinated vs. unvaccinated cohort studies as a follow-up. There is little excuse for not conducting these types of studies when there are already hundreds of thousands of completely unvaccinated children in America, including over 50,000 completely unvaccinated 2-year old children.[416]

Moreover, HHS claims in its letter that the white paper states that the "CDC has started conducting some of the studies mentioned in the white paper."[417] The white paper, however, contains no such claim.[418] Nonetheless, if true, it is troubling that this study is being undertaken by HHS's Immunization Safety Office which assists in defending against vaccine injury claims and is headed by Dr. Frank DeStefano, who is accused by his fellow CDC senior scientist of fraudulently modifying results of prior vaccine studies, including to avoid liability for HHS in Vaccine Court.[419] To be reliable, any vaccinated vs. unvaccinated study must be conducted by individuals completely independent of HHS and otherwise completely impartial. Nobody at HHS can impartially conduct a vaccine safety study because a finding that childhood vaccines cause any serious harm would result in serious

[415] The white paper also suggests "minor injuries" as a control because "[t]here is no plausible biologic pathway by which vaccines could cause these minor injuries"; but if vaccination causes neurological disorders which render children more prone to injury, vaccinated children would have a higher rate of minor injuries. https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

[416] https://www.cdc.gov/mmwr/volumes/67/wr/mm6740a4.htm

[417] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

[418] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

[419] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio; http://www.rescuepost.com/files/william-thompson-statement-27-august-2014-3.pdf

reputational harm to HHS, would conflict with its mission to assure high vaccine uptake, and would be used as evidence against HHS in Vaccine Court where HHS is charged to defend against claims of vaccine injury.

This concern is even more acute given that HHS really does not know the actual safety profile of each childhood vaccine nor its childhood vaccine schedule. As HHS acknowledges in its white paper: "the field of vaccine schedule safety is in its infancy."[420]

C. HHS's Bias Leaves It Unable to See Glaring Safety Signals

HHS then states that "should signals arise that there may be a need for investigation," HHS would then conduct an appropriate vaccinated vs unvaccinated study.[421] Let us provide HHS with a few such signals.

A very bright vaccine safety signal is the fact that HHS knows that less than 1% of adverse events occurring after vaccination are reported to VAERS and HHS knows that there were 261,294 adverse vaccine events reported to VAERS in the last five years.[422]

The following finding from the School of Public Health at Jackson State University is another bright flashing vaccine safety signal: 33% of vaccinated preterm babies had a neurodevelopmental disorder while 0% of the unvaccinated preterm babies had a neurodevelopmental disorder; and another pilot study by the same group found that vaccinated children, compared to unvaccinated children (receiving no vaccines), had an increased risk of 390% for allergies, 420% for ADHD, 420% for autism, 290% for eczema, 520% for learning disabilities, and 370% for any neuro-developmental delay.[423]

Another clear vaccine safety signal is the body of replicated peer-reviewed studies evidencing that that aluminum adjuvant in vaccines injected into the muscle tissue of lab animals are phagocytized by macrophages, transported to their brains and cause neurological impairments.[424]

---

[420] https://www.cdc.gov/mmwr/volumes/67/wr/mm6740a4.htm

[421] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf

[422] https://wonder.cdc.gov/vaers.html

[423] http://www.oatext.com/pdf/JTS-3-186.pdf; http://www.oatext.com/pdf/JTS-3-187.pdf

[424] http://icandecide.org/white-papers/ICAN-AluminumAdjuvant-Autism.pdf. Macrophages phagocytize (ingest) aluminum adjuvant (**AA**): https://www.ncbi.nlm.nih.gov/pubmed/15297065; https://www.ncbi.nlm.nih.gov/pubmed/18496530. Macrophages transport material into the brain: https://www.ncbi.nlm.nih.gov/pubmed/27213597; https://www.ncbi.nlm.nih.gov/pubmed/21348773; https://www.ncbi.nlm.nih.gov/pubmed/27115998; https://www.ncbi.nlm.nih.gov/pubmed/27213597. AA transport to brain: https://www.ncbi.nlm.nih.gov/pubmed/26384437; https://www.ncbi.nlm.nih.gov/pubmed/27908630; https://www.ncbi.nlm.nih.gov/pubmed/23557144. AA causes neuro impairment: https://www.ncbi.nlm.nih.gov/pubmed/27908630; https://www.ncbi.nlm.nih.gov/pubmed/19740540; https://www.ncbi.nlm.nih.gov/pubmed/23932735. Macrophages infiltrate the brain in autism: https://www.ncbi.nlm.nih.gov/pubmed/16401547; https://www.ncbi.nlm.nih.gov/pubmed/15546155; https://www.ncbi.nlm.nih.gov/pubmed/28167942; https://www.ncbi.nlm.nih.gov/pubmed/24951035.

Another vaccine safety signal is that clinical trials comparing health outcomes in two vaccinated groups typically find that both groups have significant rates of serious adverse events which exceed what would be expected in the general population.[425] The fact that no HHS licensed vaccine, save one, has been safety tested for use in children in a placebo-controlled trial prior to licensure makes each of these safety signals burn even brighter.[426]

The greatest vaccine safety signal may be the ever-growing percentage of Americans refusing to vaccinate their children. According to HHS, between 2001 and 2017 the number of completely unvaccinated two-year-old children in America has increased by 433%.[427] One in 77 two-year old American children are now completely unvaccinated and 1 in 2 children skip one or more vaccines on HHS's childhood vaccine schedule.[428] This growth has occurred despite stricter vaccination laws and access to free vaccinations for lower income populations.

Parents declining one or more HHS recommended vaccinations for their children often have concerns about vaccine safety because they themselves, their children, or someone else close to them, has had a personal experience with a life-altering adverse event following vaccination.[429] Parents who make this informed choice, as HHS admits, are typically well-educated, and do so in the face of social stigma and exclusion; hence, they often never make this decision lightly, but rather after careful research or a personal experience with vaccine injury.[430]

The stated purpose of vaccination is to improve the overall quality of health of Americans and reduce mortality. Yet, the increase in HHS's childhood vaccine schedule over the last 30 years from 8 vaccine injections[431] to 50 vaccine injections[432] (plus 2 injections during pregnancy[433]) has occurred in lockstep with the increase in the rate of autoimmune, developmental and neurological disorders in children from 12.8% to 54%.[434] HHS has no explanation for why U.S. children today are plagued with a chronic disease and disability epidemic.

---

[425] For examples see Sections I and IV above.
[426] See Section I above.
[427] https://www.cdc.gov/mmwr/volumes/67/wr/mm6740a4.htm
[428] https://www.cdc.gov/mmwr/volumes/67/wr/mm6740a4.htm; https://stacks.cdc.gov/view/cdc/59415
[429] https://www.ncbi.nlm.nih.gov/pubmed/25200366
[430] https://www.ncbi.nlm.nih.gov/pubmed/18816357; https://www.ncbi.nlm.nih.gov/pubmed/28578210; https://www.cnn.com/2015/02/03/health/the-unvaccinated/index.html
[431] https://www.cdc.gov/vaccines/schedules/images/schedule1989s.jpg (OPV is given orally)
[432] https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html#schedule (Rotavirus is given orally. Assumes 4-dose Hib series, 3-dose HPV series, and no combination vaccines; but even with combination vaccines still have a total of 40 injections.)
[433] https://www.cdc.gov/vaccines/pregnancy/downloads/immunizations-preg-chart.pdf
[434] Compare https://www.cdc.gov/vaccines/schedules/images/schedule1983s.jpg with https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

This as yet unexplained explosion in chronic disease and disability among American children, which coincides with the rapid increase in the numbers of vaccinations given to infants and children in the first six years of life, is a neon vaccine safety signal that demands methodologically sound studies to rule out vaccines or the HHS childhood vaccine schedule as a contributing cause. It is accepted science that adverse responses to vaccination can lead to certain chronic disorders, including autoimmune, developmental and neurological disorders – it is only the rate at which this occurs that is either disputed or admittedly unknown.[435] Given that the incidence of chronic diseases and disabilities is at an all-time high among children, especially among babies born healthy who then regress into chronic poor health in early childhood, it is high time to determine if vaccination is a contributing factor for this decline in overall childhood health.

HHS's response fails to provide evidence that these chronic diseases and disabilities are not caused by vaccination. If HHS does not know, then HHS cannot assess whether its childhood vaccine schedule – which produces a financial windfall to pharmaceutical companies[436] and the HHS agencies and employees that receive royalties from childhood vaccine sales[437] – is causing more harm than good. As discussed above, the flawed clinical trials that HHS relies upon to license vaccines are incapable of scientifically determining whether vaccines cause any of the chronic illnesses and developmental disorders that have steadily risen among American children during the past three decades. Despite this gap in safety, and despite the growing chorus of vaccine harm from parents – which is a major reason vaccine rates are declining – HHS defiantly continues to claim there are no vaccine safety signals.

Doctors have long been trained to listen to their patients, and studies have repeatedly shown that parents are the best source of information about their children and provide highly accurate information for detecting symptoms of and addressing developmental and behavioral problems.[438] HHS should take heed of this age-old wisdom and listen to the growing number of parents who, as the vaccine schedule has expanded, have reported that they observed their children regress into poor health after vaccination, including losing

---

[435] Among other sources: https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf; https://www.nap.edu/read/1815/chapter/2#7; https://www.nap.edu/read/2138/chapter/2#11; https://www.nap.edu/read/13164/chapter/2#2; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/; children must "prove that the vaccine was the cause" for all off-Table vaccine injuries, https://www.ncbi.nlm.nih.gov/nlmcatalog/101633437, 98% of vaccine injury claims are off-Table, http://www.gao.gov/assets/670/667136.pdf, and partial database of off-Table vaccine injury awards, https://www.uscfc.uscourts.gov/aggregator/sources/7; see studies compiled in this white paper: http://icandecide.org/white-papers/ICAN-AluminumAdjuvant-Autism.pdf; conditions listed in Appendix B are reported in one or more pediatric vaccine package inserts, https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm, because, as required by federal law, there is a "basis to believe there is a causal relationship between the drug and the occurrence of the adverse event," 21 C.F.R. 201.57.

[436] https://investors.pfizer.com/financials/annual-reports/default.aspx; https://investors.merck.com/financials/sec-filings/default.aspx; https://www.gsk.com/media/4751/annual-report.pdf; https://www.sanofi.com/en/investors/reports-and-publications/

[437] https://www.ott.nih.gov/royalty/information-nih-inventors; https://www.ott.nih.gov/resources; https://www.ott.nih.gov/reportsstats/top-20-commercially-successful-inventions; https://www.ott.nih.gov/sites/default/files/documents/pdfs/AR2017.pdf; https://www.ott.nih.gov/news/nih-technology-licensed-merck-hpv-vaccine; https://www.ott.nih.gov/reportsstats/hhs-licensed-products-approved-fda

[438] https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1440-1754.1999.00342.x

previously met cognitive and physical milestones and suffering changes in personality and behavior. If HHS wants to prove them wrong, it needs to produce real science showing the actual safety of each childhood vaccine and HHS's childhood vaccine schedule. That science demands, at the very least, a properly sized and controlled prospective study comparing health outcomes in vaccinated and completely unvaccinated children.

VIII. HHS REFUSES TO COMMIT TO REDUCING CONFLICTS OF INTEREST

Our opening letter asserted numerous incriminating conflicts of interest at HHS and outright misconduct by HHS officials with regard to fulfilling its critical vaccine safety duties. HHS's response letter does not contest any of these. This may be because almost all of the conflicts of interest and misconduct we referenced in our opening letter were originally identified in congressional and other governmental reports. These reports found, for example, that the "overwhelming majority of members [of HHS's vaccine licensing committee], both voting members and consultants, have substantial ties to the pharmaceutical industry" [439] and that the process of recommending vaccines at HHS reflected "a system where government officials make crucial decisions affecting American children without the advice and consent of the governed."[440] All of these findings, as noted, remained unchallenged in HHS's response.

Many of these issues arise because HHS, *on the one hand*, is required to promote universal vaccine uptake and to defend vaccines from any claim of harm in Vaccine Court and, *on the other hand*, is responsible for the conflicting duty of assuring vaccine safety. Unfortunately, HHS's vaccine uptake/defense duties have suffocated its vaccine safety duties. We therefore suggested a number of ways in which some balance between these conflicting duties could be created.

Despite not contesting the serious conflicts of interest and misconduct regarding vaccine safety at HHS, your response rejects every single suggestion. Without drastic change, HHS's critical statutory duty to ensure vaccine safety will remain buried by HHS's vaccine uptake/defense duties. Based on HHS's response, the only real solution appears clear: remove vaccine safety into an entirely independent board that has no responsibility for vaccine uptake or defense.

A. HHS's Failure To Perform Its Vaccine Safety Duties

Recent admissions by HHS bring into sharp focus HHS's failure to perform its vaccine safety duties under the 1986 Act. As HHS is aware, when Congress in 1986 granted economic immunity to pharmaceutical companies for vaccine injuries, the financial

[439] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf
[440] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf

incentive for pharmaceutical companies to be accountable for and assure vaccine safety was eliminated.[441] Recognizing the unprecedented elimination of this market force, Congress in 1986 made HHS directly responsible for virtually every aspect of assuring vaccine safety.[442] Congress codified this obligation in 42 U.S.C. § 300aa-27 entitled "Mandate for Safer Childhood Vaccines" (the **Mandate**).

This Mandate underpins all vaccine safety in this country and has three simple parts. The following is a copy of the entire Mandate:

> **(a) General rule.** In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary [of HHS] shall— (1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on December 22, 1987, and promote the refinement of such vaccines, and (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.
>
> **(b) Task force.** (1) The Secretary shall establish a task force on safer childhood vaccines which shall consist of the Director of the National Institutes of Health, the Commissioner of the Food and Drug Administration, and the Director of the Centers for Disease Control. (2) The Director of the National Institutes of Health shall serve as chairman of the task force. (3) In consultation with the Advisory Commission on Childhood Vaccines, the task force shall prepare recommendations to the Secretary concerning implementation of the requirements of subsection (a) of this section.
>
> **(c) Report.** Within 2 years after December 22, 1987, and periodically thereafter, the Secretary shall prepare and transmit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the actions taken pursuant to subsection (a) of this section during the preceding 2-year period.[443]

[441] 42 U.S.C. § 300aa-10; 42 U.S.C. § 300aa-11
[442] 42 U.S.C. § 300aa-27
[443] 42 U.S.C. § 300aa-27

The first part of the Mandate requires the Secretary of HHS to assure and improve every aspect of vaccine safety.[444] The second part creates the Task Force on Safer Childhood Vaccines (the **Task Force**), comprised of the heads of NIH, FDA and CDC, and requires the Task Force to make recommendations to the Secretary of HHS on how to improve vaccine safety.[445] The third part requires the Secretary of HHS to submit a report to Congress every two years, starting in 1989, detailing the improvements made to vaccine safety in the preceding two years.[446]

Despite these clear requirements, HHS has failed to fulfill any of its duties under the Mandate. After our repeated demands for copies of Task Force recommendations, HHS finally admitted that the Task Force was disbanded in 1998. After we were forced to file a federal lawsuit to obtain copies of biennial vaccine safety reports that HHS was supposed to submit to Congress, HHS finally admitted that it has never once prepared or filed a single report as required by the Mandate.[447]

When HHS fails to accomplish the simple tasks of merely making vaccine safety recommendations (required by part two of the Mandate) and preparing biennial vaccine safety reports to Congress (required by part three of the Mandate), it is unsurprising it has failed to conduct the difficult work required by part one of the Mandate to actually improve vaccine safety. Indeed, the substance of our respective letters make it evident that HHS has failed to perform its basic vaccine safety duties.[448]

B. HHS Must Demand Congress Vest Vaccine Safety in an Independent Board

In creating our system of government, our Founding Fathers recognized that governmental entities in powerful positions inherently have a difficult time regulating themselves. Therefore, a system of checks and balances was instituted in our system of government that has served the nation well for more than two centuries. However, this system of checks and balances has been eliminated when it comes to vaccine safety.

Given that the industry has virtually no financial liability for harms caused by vaccines, and the government department responsible for ensuring vaccine safety is driven by the need to assure vaccine uptake/defense, there is no check and balance to provide any

---

[444] 42 U.S.C. § 300aa-27

[445] 42 U.S.C. § 300aa-27

[446] 42 U.S.C. § 300aa-27

[447] http://icandecide.org/government/ICAN-HHS-Stipulated-Order-July-2018.pdf

[448] Not only has HHS abdicated its vaccine safety duties, it is apparently comfortable with its incestuous relationship with the vaccine makers it is supposed to be regulating. For example, the first HHS vaccine committee (ACIP) meeting that ICAN attended began with an honorary ceremony in which ACIP announced it had engraved the name of a decades long pharmaceutical executive, Dr. Stanley Plotkin (whose conflicts are discussed above), on the gavel used at ACIP. https://www.youtube.com/watch?v=AsOSF5hqCQc&t=356s&index=25&list=PLvrp9iOILTQb6D9e1YZWpbUvzfptNMKx2 ACIP even announced, to applause, that "all of us have been influenced" by Dr. Plotkin. This event speaks to the true ethos at HHS regarding pharmaceutical company involvement and influence upon HHS's vaccine work and policy, despite the regulations HHS cites purportedly seeking to prevent such conflicts.

level of assurance regarding vaccine safety. There is only an almost militant drive by HHS to promote vaccines, require their use and defend vaccines against any claim they cause harm, including as the defendant in the Vaccine Court.[449]

Product liability attorneys provide a critical check in ensuring unsafe products are either improved or eliminated from the market through civil lawsuits. But when it comes to childhood vaccines, this critical check was eliminated when product liability attorneys were neutralized by the grant of economic immunity to vaccine makers for vaccine injuries.[450] Without economic liability for vaccine injuries, pharmaceutical companies' fiduciary duty to their shareholders to maximize profits dictates licensing and marketing as many vaccines as possible, irrespective of their safety profile.

Congress sought to fill this void in vaccine safety (which it had created) by simultaneously making HHS legally responsible to assure vaccine safety. However, in hindsight, HHS was doomed to fail in assuring vaccine safety because HHS was simultaneously given the obligation to defend against every claim in Vaccine Court and assure high vaccine uptake.[451]

Moreover, HHS has become a "captive agency" co-opted by the very vaccine manufacturers it is supposed to be regulating (termed "agency capture" in academia).[452] There is simply no government agency pushing to ensure vaccine safety. On the other hand, there are billions of dollars spent by HHS and pharmaceutical companies every year to develop and promote vaccines, conduct studies to expand vaccine use, and discredit the scientists and medical professionals who testify on behalf of vaccine injured children in Vaccine Court or raise legitimate safety concerns regarding vaccines.[453]

When a department, such as HHS, is responsible for both promoting an industry and for ensuring the safety of that industry's products/activities, there is well settled precedent for separating these functions. HHS can learn from these precedents. For example, to avoid

---

[449] https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf (Congressional report describing how the 1986 Act gave HHS the authority to set the rules for the Vaccine Injury Compensation Program (**VICP**) and that HHS used this authority to change the rules of the VICP in its favor so it can more readily defeat vaccine injury claims. Indeed, the 1986 Act created a Vaccine Injury Table (the **Table**) which quickly compensated certain common vaccine injuries. If the petitioner suffered a Table injury, the burden shifted to HHS to prove the vaccine did not cause the injury. After passage of the 1986 Act, almost 90 percent of claims were Table claims and settled quickly. Soon after, in 1995 and 1997, HHS amended the Table such that 98% of new claims are off-Table. This change greatly increased the difficulty of obtaining compensation for vaccine injuries; and while HHS changed the VICP rules in its favor, "DOJ attorneys make full use of the apparently limitless resources available to them," "pursued aggressive defenses in compensation cases," "establish[ed] a cadre of attorneys specializing in vaccine injury" and "an expert witness program to challenge claims.")

[450] https://www.ncbi.nlm.nih.gov/pubmed/12923993; https://media2.mofo.com/documents/101200-ch55.pdf

[451] 42 U.S.C. § 300aa-1; 42 U.S.C. § 300aa-2; 42 U.S.C. § 300aa-10; 42 U.S.C. § 300aa-11; 42 U.S.C. § 300aa-14; 42 U.S.C. § 300aa-26; 42 U.S.C. § 300aa-27

[452] https://onlinelibrary.wiley.com/doi/abs/10.1111/rego.12209

[453] https://www.hhs.gov/about/budget/index.html; https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf; https://www.uscfc.uscourts.gov/aggregator/sources/7; https://www.ncbi.nlm.nih.gov/pubmed/29564139; https://investors.pfizer.com/financials/annual-reports/default.aspx; https://investors.merck.com/financials/sec-filings/default.aspx; https://www.gsk.com/media/4751/annual-report.pdf; https://www.sanofi.com/en/investors/reports-and-publications/

conflicts of interest inherent in having one department promote transportation as well as assure its safety, the responsibility for transportation safety was transferred from the Department of Transportation to the independent National Transportation Safety Board (**NTSB**).[454] Similarly, to avoid conflicts in having one department promote nuclear energy and assure its safety, the safety function was transferred to the independent Nuclear Regulatory Commission (**NRC**).[455] In the same manner, HHS should support removing vaccine safety from HHS altogether into an entirely independent board, as was done with the NTSB and NRC. In fact, using the NTSB as a model, vaccine researchers from Johns Hopkins University have advocated, as early as 2004, for removing vaccine safety from HHS and placing into an entirely independent National Vaccine Safety Board.[456]

There are, in fact, additional and even more compelling reasons for removing vaccine safety duties from HHS than there were for creating the NTSB and NRC. When transportation or nuclear related injuries occur, the companies causing these injuries are, to varying degrees, economically liable for the injuries. In contrast, when a vaccine injury occurs, the companies causing these injuries are effectively economically immune from liability under the 1986 Act.[457] Hence, unlike the NTSB and NRC, where the companies they regulate still have an economic incentive to assure safety, there is no such economic incentive for vaccine makers.[458] As such, unlike nuclear and transportation safety where the onus of safety still remains with industry, the onus of vaccine safety falls solely on the shoulders of HHS, making its mission to assure safety in many ways far more critical than the safety missions of the NTSB and NRC.

The NTSB and NRC also only assist victims of injury by the transportation and nuclear industries. In contrast, HHS is supposed to play the dual and conflicting roles of identifying and preventing injuries to children from vaccination while simultaneously serving as the defendant in Vaccine Court where, represented by the DOJ, it is statutorily required to defend against any claim that a vaccine injured a child, which HHS does vigorously.[459]

Thus, any study or admission by HHS that would support that a vaccine caused even a potential harm could be used against HHS in the Vaccine Court. Even HHS's Immunization Safety Office, which is responsible for vaccine safety, provides ongoing assistance to HHS's Division of Vaccine Injury Compensation, which is responsible for defending against claims of vaccine injury, in order to defeat claims in Vaccine Court.[460] It

---

[454] https://www.ntsb.gov/about/history/pages/default.aspx
[455] https://www.nrc.gov/about-nrc/history.html
[456] https://www.ncbi.nlm.nih.gov/pubmed/15249296
[457] 42 U.S.C. § 300aa-1 et seq.; Bruesewitz v. Wyeth LLC, 562 U.S. 223 (2011)
[458] 42 U.S.C. § 300aa-1 et seq.
[459] 42 U.S.C. § 300aa-12; https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf
[460] Advisory Committee on Immunization Practices, Transcript of October 25, 2017 Presentation "Vaccine Injury: Shoulder Injury After Vaccination" available at https://www.cdc.gov/vaccines/acip/meetings/meetings-info.html

is amazing that the Immunization Safety Office is actually involved in fighting against, not for, families claiming their child was seriously injured by a vaccine. It is also unjust to demand that a child, who received vaccines based on HHS's vaccine schedule, prove how one or more of those vaccines caused his or her injury (i.e., prove "causation") in Vaccine Court while fighting against HHS; all while (as discussed above) HHS has not performed the science to understand how and why vaccines cause injury despite being statutorily tasked with that job.[461]

These structural conflicts make removal of vaccine safety from HHS far more compelling than the removal of transportation safety and nuclear safety to the NTSB and NRC.

The above is just a small part of why Congress concluded that the system at HHS for recommending and promoting vaccines reflects "a system where government officials make crucial decisions affecting American children without the advice and consent of the governed."[462] A December 2009 report by HHS's Office of the Inspector General again found that the "CDC had a systemic lack of oversight of the ethics program for [committee members]," and that, for example, "[m]ost of the experts who served on advisory panels in 2007 to evaluate vaccines for flu and cervical cancer had potential conflicts that were never resolved."[463] HHS's response letter also does not contest that CDC does accept funding from the pharmaceutical industry, directly and indirectly, despite claiming otherwise on its website, and that key vaccine program personnel are reluctant to take actions that would diminish their chances of securing lucrative private sector jobs with vaccine manufacturers.[464]

Many parents, physicians and scientists, as well as lawmakers, are legitimately concerned about the foregoing, including HHS's long running failure to fulfill its essential vaccine safety duties. Their concern is not rooted in a wild conspiracy or a belief of insidious intent. Rather, it is rooted in the idea that having HHS responsible for promoting vaccines and defending vaccines, including in Vaccine Court, is directly at odds with ensuring vaccine safety, especially where any finding that a childhood vaccine can cause serious harm could result in HHS having to pay damages in Vaccine Court as well as serious reputational

---

[461] This was not what Congress intended in passing the 1986 Act. Instead, the 1986 Act created a Vaccine Injury Table (the "**Table**") which was intended to permit the Vaccine Court to quickly compensate certain common vaccine injuries. 42 U.S.C. § 300aa-12. If the child suffered an injury on the Table, the burden shifted to HHS to prove the vaccine did not cause the injury. 42 U.S.C. § 300aa-13. After passage of the 1986 Act, almost 90% of claims were Table claims and quickly settled. Stevens v. Secretary of HHS, No. 99-594V (Office of Special Masters 2001). However, in 1995 and 1997, HHS amended the Table such that now 98% of new claims are off-Table. http://www.gao.gov/assets/670/667136.pdf. As a result, injured children must now almost always prove "causation" – the biological mechanism by which the vaccine injured the child. https://www.ncbi.nlm.nih.gov/nlmcatalog/101633437 ("Persons alleging a condition not included in the table … must prove that the vaccine was the cause.") Requiring an injured child to prove causation adds insult to injury because had HHS conducted the safety science it demands as proof in Vaccine Court, the child's injury may have been avoided altogether.

[462] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf

[463] https://oig.hhs.gov/oei/reports/oei-04-07-00260.pdf; http://www.nytimes.com/2009/12/18/health/policy/18cdc.html

[464] http://www.bmj.com/content/350/bmj.h2362

harm. HHS has serious conflicts and powerful disincentives which create institutional gridlock that prevent HHS from initiating, admitting or publishing any research that would support a claim that any childhood vaccine or HHS's childhood vaccine schedule causes serious injury or chronic illness in children.

HHS's response letter makes clear that these concerns are not only well founded, but worse than alleged in our opening letter.[465]

IX. VSD AND PRISM

HHS's response asserted that it investigates vaccine safety post-licensure using the Vaccine Safety Datalink (**VSD**) and the Post-licensure Rapid Immunization Safety Monitoring System (**PRISM**). While these could be helpful in assessing vaccine safety, that is not currently the case.

As for the VSD, instead of being used to improve safety, it is used as a tool to silence vaccine critics and expand vaccine recommendations, even for uses not licensed by the FDA. First, the VSD was once maintained at HHS but when scientists began to access the VSD to conduct studies which revealed vaccine harm, HHS purposely moved the VSD to a health industry trade association starting in 2001 to avoid having the VSD data subject to FOIA, and to otherwise assure that only the scientists and studies it approves utilize the VSD.[466]

Second, when a VSD study is conducted by HHS, in violation of basic scientific standards and process, the underlying raw data is almost never available for inspection by the public and other scientists.[467] Refusal to make this data available raises serious concerns regarding reproducibility and transparency. HHS regulations in fact provide severe penalties if researchers, using HHS funding, refuse to share data underlying their studies, but HHS does not apply this same standard to their own VSD studies.[468]

Third, the secret studies that HHS performs using the VSD with secret data are virtually all squarely aimed at increasing vaccine uptake, even for uses and in populations not approved by the FDA. For example, a plurality of the nineteen VSD studies conducted

---

[465] Our opening letter also highlighted that HHS is required to assure that any "health care provider who administers a vaccine … shall record … in such person's permanent medical record … the vaccine manufacturer and lot number." (42 U.S.C. §§ 300aa-25(a)) We therefore asked in our opening letter that HHS: "Please explain what HHS has done to assure that health care providers record the manufacturer and lot number for each vaccine they administer?" HHS's response does little more than restate HHS's requirement, and does not show it does anything to enforce this requirement. This is another dereliction of HHS's vaccine safety duties. This statutory obligation could not be any clearer. If HHS will not do anything of substance to assure the simple requirement of recording lot information, so that "hot lots" can be identified, there is little hope that HHS will fulfill its far more complex vaccine safety duties.

[466] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4708093/

[467] https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/accessing-data.html

[468] https://www.federalregister.gov/documents/2016/09/21/2016-22379/nih-policy-on-the-dissemination-of-nih-funded-clinical-trial-information

by HHS in 2017 involved the vaccination of pregnant women.[469] This is plainly in response to the HHS recommendation that influenza and Tdap vaccines be administered to every pregnant woman, despite the fact that these vaccines were not licensed by the FDA for use in pregnant women.[470] HHS is essentially engaging in off-label marketing that, if conducted by the vaccine manufacturer, would be illegal, and is seeking to use the VSD as an after-the-fact tool to justify this conduct.[471]

Fourth, the VSD must be retooled to assess the long-term impact of vaccination, which is the real concern the public has about vaccine safety. Indeed, HHS has acknowledged that the public stakeholders "have expressed more concerns about long-term than short-term health outcomes" and that "long-term health outcomes have been less well-studied in the context of vaccine safety," but that VSD is currently geared toward assessing short-term, and not long-term, health outcomes:

> The current safety surveillance systems such as the VSD, and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system of the Food and Drug Administration (FDA), already have extensive systems in place to assess short-term outcomes … [despite the fact] the childhood immunization schedule is essentially a long-term exposure, occurring over 18 to 24 months, [and hence] long-term adverse events may be more biologically plausible than short-term events.[472]

Fifth, it is highly inappropriate that VSD studies are conducted by HHS's Immunization Safety Office which, as discussed above, is headed by an individual accused by a Senior Scientist at HHS of fraudulently modifying results of prior vaccine studies, including for the purpose of avoiding liability for HHS in Vaccine Court.[473]

Sixth, and critically, any VSD study intended to assure the public that vaccines are safe should be designed and performed by an organization for whom a finding that a vaccine causes a serious harm would not have significant financial and/or reputational repercussions, as it would for HHS. In fact, the very HHS office that conducts VSD studies, the Immunization Safety Office, as discussed above, actively assists in defeating vaccine injury claims in Vaccine Court.

---

[469] https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/publications.html

[470] https://www.cdc.gov/vaccines/pregnancy/hcp/resources.html (advertising materials created by the CDC to promote vaccines to pregnant women); https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm (each vaccine package inserts states, in one form or another, that the safety and effectiveness of the vaccine has not been established in pregnant women)

[471] https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Downloads/off-label-marketing-factsheet.pdf

[472] https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf

[473] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio; http://www.rescuepost.com/files/william-thompson-statement-27-august-2014-3.pdf

When HHS is ready to be transparent, it should: open the VSD to all researchers; make accessible the underlying data used for all its published studies; subject itself to the same criticism of its VSD studies as other scientists; and, not have these studies conducted by anyone or any organization that participates in defending against vaccine injury claims, is accused of scientific fraud, or has any conflict of interest with finding that a vaccine causes harm. Only then can HHS finally claim the VSD is a valid research tool for improving vaccine safety. Until then, the VSD remains an improperly wielded government tool, like the KGB's Mitrokhin Archive waiting for someone from HHS to defect and share the VSD data with the scientific community.

As for PRISM, putting aside its very limited use, instead of being used to improve vaccine safety, it is also wielded by HHS to silence vaccine critics and expand vaccine recommendations for uses not licensed by the FDA. For example, every single assessment conducted in PRISM in 2018 was conducted to provide after-the-fact support for HHS's vigorous marketing campaign aimed at assuring that every pregnant woman in America receives an influenza vaccine.[474] As discussed above, despite the fact the FDA has not licensed any influenza vaccine for use in pregnant women, HHS has been recommending and promoting this off-label use to pregnant women for a decade.

It is only after HHS could no longer ignore the mounting vaccine injury claims by pregnant women and independent studies finding serious safety signals regarding the risks of vaccinating pregnant women, that HHS used VSD and PRISM to "prove" the safety of its prior pregnancy vaccine use recommendation. But these efforts are plainly not about assuring vaccine safety. If that were the goal, these safety studies would have been conducted before HHS promoted administering influenza vaccine to all pregnant women. Rather, it is a transparent effort to silence recent and growing criticism of its off-label marketing of this vaccine to pregnant women. After vigorously promoting the flu shots to pregnant women for a decade, is HHS really going to publish science that requires it to backtrack and admit: "oops, sorry, actually, it is not safe to inject pregnant women with the flu shot."

Like the VSD, it is unlikely HHS will use PRISM to publish a study that confirms any serious widespread harm from vaccination. If it did, HHS would be developing the very science that would then be used against it in Vaccine Court, potentially resulting in crippling financial liability as well as loss of reputation. This is why HHS's Vaccine Safety Office, instead of working to prevent and obtain compensation for vaccine injuries and deaths, assists HHS's office responsible for fighting against the claims of vaccine injured plaintiffs

[474] https://www.sentinelinitiative.org/vaccines-blood-biologics/assessments

in Vaccine Court. HHS is so blind to this obvious conflict that it openly bragged about this collaboration at a public ACIP meeting held in October 2017.[475]

The VSD and PRISM could be useful tools for assessing vaccine safety (after the baseline safety profile of HHS's childhood vaccine schedule is established in properly sized and controlled trials), but the studies conducted with these systems must be designed and executed by individuals and organizations without conflicts of interest and bias with regard to assessing vaccine safety. Such studies should certainly not be conducted by an organization that could suffer serious financial and reputational harm if it confirms that one or more childhood vaccines can cause serious injury. For example, finding that vaccines cause 1 in 5 cases of either allergic rhinitis, ADHD, learning disabilities or neurodevelopmental delay, all of which preliminary science has shown can be caused by vaccination,[476] would result in trillions of dollars of liability and a loss of public confidence in HHS and its vaccine schedule.

As explained by a renowned professor in the Center for Bioethics, Harvard School of Medicine, member of the Institute of Medicine, and former editor-in-chief of the New England Journal of Medicine:

> It is no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of *The New England Journal of Medicine*. …[477]

For these and other reasons discussed above, it is entirely inappropriate to have HHS manage and control VSD and PRISM. These health database platforms are paid for by the American public and should be open to every scientist in this country to conduct studies without any barrier and without requiring any permission from HHS. If HHS truly believes that vaccines are "safe and effective," it should immediately make available to the public and scientific community, as it does with VAERS, the deidentified data in the VSD and let that data speak for itself.

Conclusion

Instead of focusing on defending pharmaceutical companies and their products, including in Vaccine Court, HHS should be focused on protecting and defending children

[475] Advisory Committee on Immunization Practices, Transcript of October 25, 2017 Presentation "Vaccine Injury: Shoulder Injury After Vaccination" available at https://www.cdc.gov/vaccines/acip/meetings/meetings-info.html
[476] http://www.oatext.com/pdf/JTS-3-186.pdf
[477] https://www.nybooks.com/articles/2009/01/15/drug-companies-doctorsa-story-of-corruption/

from vaccine injuries. Pharmaceutical companies are well organized and funded. Parents of current and future vaccine injured children, the citizens the Government is supposed to serve, are not.

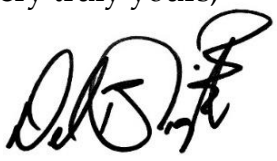
Since vaccine products are injected dozens of times into nearly every baby and child in America and are typically required by law to attend school, they should be tested for safety prior to licensure in extremely well designed clinical trials. Instead the opposite is true. Without impeccable clinical trials—with rigorous methods, large sample sizes, true placebo controls, and extended periods of observation for vaccine injury—yielding results which demonstrate that the benefits of vaccination clearly outweigh the harms, the large-scale vaccination program in this country cannot be ethically justified.

Even absent an ethical imperative, HHS's responsibility for assuring vaccine safety is required by federal law. HHS's response letter seeks to create the impression that there exists a complete understanding of the safety profile of each pediatric vaccine and HHS's childhood vaccine schedule, and that there is almost nothing left for HHS to do to assure vaccine safety. We request that HHS carefully consider all of the information provided above, which is nearly entirely grounded in and anchored by citations to HHS's own publications.

It is our hope that HHS will rise above its internal gridlock and inherent conflicts of interest, and take this opportunity to seriously consider the safety of pediatric vaccines and its childhood vaccine schedule.

We await your response to each of the points raised above and to the questions listed in Appendix A below.

Very truly yours,



Del Bigtree
President

Enclosures: Appendices A and B.[478]

[478] Appendix A of our initial letter, dated October 12, 2017, is amended to add Hope Inc. Academy, Medical Freedom Nevada, Hope from Holly, Educate.Advocate., Autism is Medical, Inc., Oregonians for Medical Freedom, Thinking Moms Revolution, Vaccine Freedom Utah, and Your Health Freedom.

APPENDIX A

QUESTIONS REGARDING VACCINE SAFETY

1. CLINICAL TRIALS

a. Please list each vaccine product that is currently recommended for routine use in children which was licensed for use in children based on a placebo-controlled clinical trial. For each vaccine product listed, please provide the clinical trial report supporting that a "placebo," as defined at www.cdc.gov/vaccines/terms/glossary.html, was used.

b. Please list each vaccine product that is currently recommended for routine use in children which was licensed for use in children based on a clinical trial that used an "active control" previously licensed for use in children based on a placebo-controlled clinical trial. For each vaccine product listed, please provide the clinical trial report supporting that a "placebo," as defined at www.cdc.gov/vaccines/terms/glossary.html, was used.

c. Will HHS henceforth require a placebo-controlled (saline injection) properly-powered (sufficient children) long-term (reviews safety for at least three years or until age eight, whichever is longer) clinical trial prior to licensing any new vaccine product for which no other vaccine exists for the target disease?

2. VACCINES INJECTED DURING THE FIRST 6-MONTHS OF LIFE

a. For each clinical trial relied upon to license any injectable vaccine product HHS currently recommends for routine use in children between birth and six-months of age, please identify (i) the control used and (ii) the trial's safety review period, by completing the following chart and please provide supporting documentation:

Licensed Vaccine Product	Control	Safety Review Period: Solicited Reactions	Safety Review Period: Unsolicited Reactions
Recombivax HB			
Engerix-B			
ActHIB			
PedvaxHIB			
Hiberix			
Infanrix			
Daptacel			
Ipol			
Prevnar 13			
Pediarix			
Pentacel			

b. Please provide the clinical trial report(s) that reflect the cumulative safety profile, by ten years of age, of injecting approximately 22 vaccine doses into babies during the first six months of life, including the rate of any autoimmune, neurological or developmental disorders.

c. Please provide the clinical trial report(s) that reflect the cumulative safety profile, by ten years of age, of injecting approximately 35 vaccine doses into babies and toddlers during the first two-years of life, including the rate of any autoimmune, neurological or developmental disorders.

3. VACCINES INJECTED INTO PREGNANT WOMEN

a. Please provide the clinical trial report(s) relied upon by HHS when licensing influenza and Tdap vaccines for use by pregnant women.

b. Is a pharmaceutical company permitted to advertise or promote the influenza or Tdap vaccines it manufactures to pregnant women? If not, why not?

4. SPECIFIC VACCINES

c. Is it acceptable to inject a healthy baby with a product that contains one or more known or suspected neurotoxic or cytotoxic substances where its licensure is based on a trial that had no control and a short safety review period?

d. Please identify and provide a copy of any placebo-controlled trial with a safety review period longer than one week that HHS relied upon when it recommended that every baby in this country receive either Recombivax HB or Engerix-B on the first day of life.

e. Please advise if HHS disputes that during the Gardasil trials the rate of girls and women 9 through 26 years of age who reported an incident condition potentially indicative of a systemic autoimmune disorder was 2.3% in the group that received Gardasil, 2.3% in the group that received AAHS Control, and 0% for the group that received Saline Placebo.

f. Please explain why it was considered ethical to inject controls during the clinical trials for (i) Gardasil with 225 mcg or 450 mcg of Amorphous Aluminum Hydroxyphosphate Sulfate (AAHS) when it has no known therapeutic benefit? (ii) Varivax with 45 mg of neomycin when neomycin is only licensed for topical and oral use?

5. POST-LICENSURE SAFETY

a. After a Harvard Pilgrim Health Care study, conducted pursuant to a grant from an HHS agency, developed a program which automatically identified and generated reports of possible vaccine reactions, please explain why HHS failed to cooperate with Harvard to automate submission of these reports to VAERS.

b. For each vaccine-injury pair for which the IOM, in its 1994 and 2011 reports, could not determine whether or not there is a causal relationship, please list the precise vaccine-injury pairs for which HHS has since determined whether there is a causal relationship. For each vaccine-injury pair identified, please specify HHS's finding regarding causation and provide documentary support.

c. Please list each vaccine on HHS's childhood vaccine schedule that has been evaluated for its (i) carcinogenic potential, (ii) mutagenic potential, or (iii) potential to impair fertility. For each vaccine listed, please identify for which of these three potentials it has been evaluated and provide documentary support.

d. Please identify the specific studies, by title, author and year, which HHS has conducted to determine specific biomarkers or other predictive criteria which can be used to identify whether a given child will suffer a serious vaccine injury.

e. Please provide the deidentified datasets from the following study relating to autism and vaccines in which HHS was involved so that we and the scientific community can analyze the data: https://www.ncbi.nlm.nih.gov/pubmed/?term=29582071

f. Please advise if HHS will forthwith provide public access to the deidentified datasets within the VSD so that all researchers can conduct vaccine safety studies without requiring any permission or approval from HHS or anyone else. Putting aside that taxpayers support the VSD, agreeing to such transparency would accord with CDC's claim that it "embraces intellectual honesty and transparency in its release of information to fully empower public decision."[479]

g. The following white paper provides the peer reviewed scientific support for how aluminum adjuvants injected into the body travel to the brain, can cause IL-6 production and microglial activation in the brain, and that this in turn can cause autism: http://icandecide.org/white-papers/ICAN-AluminumAdjuvant-Autism.pdf Please clearly and specifically explain which steps in this chain of causation or any other aspect of this white paper HHS disputes.

[479] https://www.cdc.gov/about/organization/communication-principles.html

6. CONFLICTS OF INTEREST

a. Please explain why HHS has never once prepared or submitted a biennial report to Congress detailing improvements in vaccine safety as required under federal law, 42 U.S.C. § 300aa-27(c).

b. Please explain why HHS disbanded the Task Force on Safer Childhood Vaccines in 1998 when this task force is mandated to exist pursuant to federal law, 42 U.S.C. § 300aa-27(b), to provide recommendations to assist the Secretary of HHS in his/her ongoing duty to fulfill HHS's vaccine safety obligations pursuant to 42 U.S.C. § 300aa-27(a).

c. Please explain why HHS would place the name of a pharmaceutical executive and consultant on the gavel of its premier vaccine committee, the Advisory Committee on Immunization Practices.

d. Will you support the removal of vaccine safety duties from HHS into an entirely independent government board, similar to the National Transportation Safety Board or the Nuclear Regulatory Commission. If not, please explain why.

APPENDIX B

The following is a *partial* list of post-licensure adverse reactions reported by consumers and physicians, and listed in the package inserts for one or more pediatric vaccines.[480] Pursuant to federal law, these adverse reactions are only listed if the vaccine's manufacturer has a basis to believe there is a causal relationship between the vaccine and the occurrence of the adverse event.[481] Indeed, Federal law is clear that this list should include "*only* those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."[482]

Immune System Disorders

Alopecia	*autoimmune skin disease causing loss of hair on the scalp and body.*
Anaphylactic Shock	*rapid onset of severe allergic reaction that causes sudden drop in blood pressure and narrowing of airway that can lead to seizures, shock, and death.*
Angioedema	*potentially life-threatening swelling underneath the skin.*
Arthritis	*painful and disabling autoimmune disease that includes joint pain, swelling and progressive stiffness in the fingers, arms, legs and wrists.*
Autoimmune Disease	*disease caused by the immune system mistakenly attacking the body's own tissue.*
Guillain-Barré Syndrome	*autoimmune disease where the immune system attacks the nerves in the legs, upper body, arms and/or face.*
Hemolytic Anemia	*red blood cells are destroyed faster than they can be replaced.*
Henoch-Schonlein Purpura	*abnormal immune response causing inflammation of microscopic blood vessels which can lead to multiple organ damage.*
Lupus Erythematosus	*autoimmune disease in which the immune system attacks multiple organs, including skin, joints, kidney, and brain.*
Multiple Sclerosis	*autoimmune disease in which the immune system attacks nerve fibers, causing them to deteriorate.*

[480] https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm
[481] 21 C.F.R. 201.57
[482] 21 C.F.R. 201.57

Myasthenia	*autoimmune disease causing chronic weakness of the skeletal muscles, including arms and legs, vision problems, and drooping eyelids or head.*
Myositis	*chronic muscle inflammation that damages the muscle fibers causing weakness, and may affect the arteries and blood vessels that pass through muscle.*
Polyarteritis Nodosa	*systemic vasculitis that affect medium-sized and small muscular arteries resulting in ruptures and other damage.*
Stevens-Johnson's Syndrome	*severe autoimmune reaction in which the top layer of skin is burned off and dies.*
Thrombocytopenia	*low blood platelet count which can result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes.*
Vasculitis	*inflammation of the blood vessels, potentially leading to loss of function of affected tissues and organ damage.*

Nervous System Disorders

Acute Disseminated Encephalomyelitis	*acute, widespread inflammation in the brain and spinal cord that damages myelin.*
Ataxia	*brain damage resulting in loss of full control of bodily movement, impaired speech, eye movement, and swallowing.*
Bell's Palsy	*disfiguring paralysis or weakness on one side of the face.*
Encephalitis	*inflammation of the brain, which can result in permanent injury.*
Encephalomyelitis	*inflammation of the brain and spinal cord.*
Encephalopathy with EEG Disturbances	*damage or malfunction of the brain with severity ranging from altered mental state to dementia, seizures and coma.*
Grand Mal Convulsion	*loss of consciousness and violent muscle contractions.*
Hypotonia	*low muscle tone.*
Hypotonic-Hypo-responsive Episode	*sudden and unexpected loss of tone, unresponsiveness and color change.*
Meningitis	*inflammation of protective membranes covering the brain and spinal cord.*

Migraine	*sudden and severe, pounding headaches, upset stomach, and sometimes disturbed vision.*
Motor Neuron Disease	*neurological disorder that destroys motor neurons that control essential voluntary muscle activity such as speaking, walking, breathing, and swallowing.*
Myelitis	*inflammation of spinal cord that can involve nerve pain, paralysis and incontinence.*
Nerve Deafness	*hearing loss from damage to the nerve that runs from the ear to the brain.*
Neuralgia	*intense painful sensation along a nerve or group of nerves.*
Neuropathy	*nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body.*
Ocular Palsies	*damage to the nerve of the eye that controls eye movement.*
Optic Neuritis	*inflammation causing eye pain and partial or complete vision loss.*
Paralysis	*inability to move part or all of the body.*
Radial Nerve and Recurrent Nerve Paralysis	*nerve injury to the radial nerve that can cause weakness or difficulty moving the wrist, hand or fingers.*
Radiculopathy	*compressed or pinched nerve.*
Retrobulbar Neuritis	*inflammation and damage to the optic nerve between the back of the eye and the brain.*
Seizures	*sudden, uncontrolled body movements and changes in behavior that occur because of abnormal electrical activity in the brain.*
Stroke	*blood flow blocked to the brain or bleeding in the brain, which can lead to brain damage, long-term disability, or death.*
Subacute Sclerosing Panencephalitis (SSPE)	*progressive neurological disorder affecting the central nervous system leading to mental deterioration, loss of motor function, and ultimately leading to a vegetative state followed by death.*
Syncope	*decrease in blood flow to the brain causing a loss of consciousness and muscle strength.*
Transverse Myelitis	*inflamed spinal cord which may result in paralysis.*

Other Disorders and Chronic Disorders

Aseptic Meningitis	*acute inflammation of the brain and spinal cord.*

Aplastic Anemia	*damage to the bone marrow that slows or shuts down the production of new blood cells.*
Cellulitis	*infection of the deep tissues of the skin and muscles that cause the skin to become warm and tender.*
Cyanosis	*bluish skin discoloration due to low oxygen saturation.*
Death	*permanent end of life.*
Deep Vein Thrombosis	*formation of a blood clot in a deep vein that can break off and block blood flow to organs.*
Diabetes Mellitus	*chronic condition affecting ability to use energy from food.*
Dysphonia	*impairment in the ability to speak.*
Epididymitis	*inflammation of the testicle tube, which can lead to abscess formation, testicular pain, painful urination, tissue death, and decreased functionality of gonads.*
Mental Disorders	*unusual thoughts, perceptions, emotions, behavior, and relationship with others.*
Myalgia	*muscle pain that can become chronic.*
Orchitis	*inflammation of one or more testicles that can cause infertility, testicular atrophy, and severe pain.*
Pancreatitis	*inflammation of the pancreas due to damage by digestive enzymes.*
Pneumonia	*infection in one or both lungs.*
Respiratory Infection	*infection of the respiratory tract.*
Retinitis	*inflammation of the retina which can permanently damage the retina, leading to blindness.*
Rhinitis	*irritation and inflammation of nasal mucous membranes impacting ability to breathe properly.*
Sudden Infant Death Syndrome	*sudden death of infant in good health.*
Tachycardia	*an abnormally rapid heart rate.*
Uveitis	*inflammation of the eye leading to vision loss.*
Vertigo	*problem with the vestibular portion of the inner ear causing dizziness.*

Footnote 21

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

JAN 18 2018

Mr. Del Bigtree
Informed Consent Action Network
10200 US HWY 290 W, Suite 301
Austin, Texas 78736

Dear Mr. Bigtree:

Acting Secretary Hargan has asked me to thank you for your letter expressing interest in vaccine safety and in and the federal policies guiding the licensing, recommendation, and safety monitoring of immunizations, and to respond to you directly.

The Department of Health and Human Services has a far-reaching mission to enhance and protect the health of all Americans. Vaccines are held to the highest standard of safety to both protect people from adverse reactions and enhance their health by preventing a number of serious diseases. I am proud to report that data show the United States currently has the safest supply in history.

I have provided responses to your specific questions in the enclosure to this letter. Thank you for the opportunity to address your concerns.

Sincerely yours,

Melinda Wharton

Melinda Wharton, MD, MPH
Acting Director, National Vaccine Program Office

Enclosure

HHS Responses to Questions and Comments from Mr. Bigtree

I would like to address a comment made in section II of your letter about pre-licensure safety review of pediatric vaccines. Contrary to statements made on page two of your letter, many pediatric vaccines have been investigated in clinical trials that included a placebo. In addition, there appears to be a misunderstanding regarding the term "solicited" adverse events. Typically, in vaccine trials, the incidence of certain specific clinical findings that might be expected after vaccination is monitored for a short period of time after vaccination. Because these events are pre-specified, they are considered to be "solicited" events. In addition, other unexpected or severe adverse events, which may occur over a longer period of time following vaccination, are also analyzed and evaluated by FDA, but because these events are not predicted prior to initiation of the study, these are not called "solicited" adverse events. Please be assured that vaccine safety is carefully examined regardless of whether there is a placebo included in the clinical trials. Once vaccines are approved, the safety is also carefully monitored, in some cases by manufacturer-conducted post-marketing studies by Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), or the Post-licensure Rapid Immunization Safety Monitoring System (PRISM), as well as other mechanisms.

(1) Please explain how HHS justifies licensing any pediatric vaccine without first conducting a long-term clinical trial in which the rate of adverse reactions is compared between the subject group and a control group receiving an inert placebo?

Inert placebo controls are not required to understand the safety profile of a new vaccine, and are thus not required. In some cases, inclusion of placebo control groups is considered unethical. Even in the absence of a placebo, control groups can be useful in evaluating whether the incidence of a specific observed adverse event exceeds that which would be expected without administration of the new vaccine. Serious adverse events are always carefully evaluated by FDA to determine potential association with vaccination regardless of their rate of incidence in the control group. In cases where an active control is used, the adverse event profile of that control group is usually known and the findings of the study are reviewed in the context of that knowledge.

(2) Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life?

Data relied upon in licensing infant use of hepatitis B vaccines is summarized in the respective package inserts. Furthermore, pediatric data from other countries and in the literature, support the safety of these vaccines in infants. The recommendation for all children to receive these vaccines was made by the Advisory Committee for

Immunization Practices. Their reasoning is summarized in a *Morbidity and Mortality Weekly Report* at https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm. Follow-up studies support the safety of infant vaccination with hepatitis B vaccines.

(3) Please explain why HHS failed to cooperate with Harvard to automate VAERS reporting? And detail any steps that HHS has taken since toward automating VAERS reporting?

On June 30, 2017, the Centers for Disease Control and Prevention (CDC) and FDA implemented a revised reporting form and a new process for submitting reports to the VAERS for non-manufacturer reports. Persons reporting adverse events are now able to use the VAERS 2.0 online reporting tool to submit reports directly online; alternatively, they may download and complete the writable and savable VAERS 2.0 form and submit it using an electronic document upload feature. Vaccine manufacturers submit VAERS reports electronically through the FDA Electronic Submissions Gateway (ESG). With VAERS 2.0 and the FDA ESG, multiple electronic options exist for VAERS reporting.

In addition, CDC is developing the next generation of spontaneous reporting mechanisms for the VAERS. Following its initial work with Harvard, CDC completed a successful proof of concept study with Harvard and other partners that takes advantage of electronic health records (EHR) and computer algorithms to facilitate direct reporting from EHR systems. You can read about that study at https://academic.oup.com/cid/article/61/6/864/451758. CDC continues to explore options to further develop this capability.

(4) Please explain any specific steps taken by HHS to improve adverse reaction reporting to VAERS?

Please see my response to question #3.

(5) For each of the 38 vaccine-injury pairs reviewed in the 1994 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please refer to the latest review of the "Safety of Vaccines Used for Routine Immunization in the United States" published in 2014 at https://www.ahrq.gov/research/findings/evidence-based-reports/vaccinestp.html. This report reviewed and accepted the findings of the 2011 Institute of Medicine report and provides an independent, systematic review of the literature published after that report on the safety of vaccines recommended for routine immunization of children, adolescents,

and adults in the United States. The report, highlighted in the July 2014 issue of *Pediatrics*, provides the most comprehensive review to date of published studies on the safety of routine vaccines recommended for children in the United States. The report concludes that the risk of rare adverse events must be weighed against the protective benefits that vaccines provide. Furthermore, the Centers for Disease Control and Prevention (CDC) has been working to address several of the vaccine-injury pairs that have been identified in the reports mentioned above. A list of CDC vaccine safety publications can be found at: https://www.cdc.gov/vaccinesafety/research/publications/index.html.

(6) For each of the 135 vaccine-injury pairs reviewed in the 2011 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please see response to question #5.

(7) Please explain what HHS has done to assure that health care providers record the manufacturer and lot number for each vaccine they administer?

Health care providers who administer vaccines covered by the National Vaccine Injury Compensation Program (VICP) are required under the National Childhood Vaccine Injury Act of 1986 (Vaccine Act), as amended, to ensure that the permanent medical record of the recipient (or a permanent office log or file) indicates the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine. This provision of the Vaccine Act applies to any vaccine for which there is a routine recommendation for childhood vaccination, even if many or most doses of the vaccine are administered to adults (e.g., influenza vaccine). In addition, the provider is required to record the edition date of the Vaccine Information Statement (VIS) distributed and the date those materials were provided.

The Advisory Committee on Immunization Practices (ACIP) also issued "General Best Practice Guidelines for Immunization" at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/records.html. This report provides information for clinicians and other health care providers about concerns that commonly arise when vaccinating persons of various ages, and includes a chapter on vaccination records that reinforces the Vaccine Act's requirement to record in the recipient's medical record (or a permanent office log or file) the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine.

(8) Please advise when HHS intends to begin conducting research to identify which children are susceptible to serious vaccine injury? If HHS believes it has commenced this research, please detail its activities regarding same?

HHS is currently supporting several initiatives that focus on advancing research on the fields of precision vaccinology (vaccine formulations tailored on the individual immune reactivity status) and adversomics (the study of vaccine adverse reactions using immunogenomics and systems biology approaches). Two examples are listed below:

- https://www.immuneprofiling.org/hipc/page/showPage?pg=about
- https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

(9) Please confirm that HHS shall forthwith remove the claim that "Vaccines Do Not Cause Autism" from the CDC website, or alternatively, please identify the specific studies on which HHS bases its blanket claim that no vaccines cause autism?

Vaccines are held to strict standards of safety. Many studies have looked at whether there is a relationship between vaccines and autism spectrum disorder (ASD). These studies continue to show that vaccines do **not** cause ASD. For more information, please refer to the literature below:

- https://www.cdc.gov/vaccinesafety/pdf/cdcstudiesonvaccinesandautism.pdf
- http://nationalacademies.org/hmd/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
- http://www.jpeds.com/article/S0022-3476(13)00144-3/pdf?ext=.pdf
  http://nationalacademies.org/HMD/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx

While there is still a lot to learn about ASD, research from public and private organizations indicate that environmental and genetic factors may increase the risk of autism, not vaccines or vaccine ingredients. HHS continues to research this issue to search for answers to better understand the risk factors and causes of this disease. Recent efforts to coordinate autism research are reflected in the "Strategic Plan for Autism Spectrum Disorder Research" by the Interagency Autism Coordinating Committee at https://iacc.hhs.gov/publications/strategic-plan/2017/.

(10) Please advise whether HHS intends to forthwith conduct adequately powered and controlled prospective as well as retrospective studies comparing total health outcomes of fully/partially vaccinated with completely unvaccinated children?

HHS tasked the Institute of Medicine (IOM) to identify research approaches, methodologies, and study designs that could address questions about the safety of the current schedule. This report is the most comprehensive examination of the immunization schedule to date and can be found at http://nationalacademies.org/HMD/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx. The IOM committee uncovered no evidence of major safety concerns associated with adherence to the childhood immunization schedule. The committee also cited ethical concerns about conducting a new study to compare the health outcomes of vaccinated children with their fully unvaccinated counterparts, as this would intentionally leave unvaccinated people and the communities they live in subject to increased risk of death and illness.

Should signals arise that there may be need for investigation, however, the report offers a framework for conducting safety research using existing or new data collection systems. One of the systems that the IOM report considered best suited to conduct these types of studies is CDC's Vaccine Safety Datalink (VSD). In response to the IOM report, CDC commissioned a white paper on the feasibility of conducting studies of the safety of the vaccine schedule in VSD. This report states, "Additionally, CDC has started conducting some of the studies mentioned in the white paper." Additional information on the white paper can be found at: https://www.cdc.gov/vaccinesafety/pdf/whitepapersafety_web.pdf.

(11) Please advise if you will:

a. prohibit conflict waivers for members of HHS's vaccine committees (ACIP, VRBPAC, NVAC & ACCV)?

HHS employs a thorough process for soliciting and vetting candidates for advisory committees to minimize any potential for financial conflicts of interest and works to identify all potential financial conflicts related to the particular matter before a committee. In accordance with 18 U.S.C. § 208(b)(1) and (b)(3), a member of an HHS vaccine advisory committee may be granted a waiver to allow individuals with potentially conflicting financial interests to participate in meetings where it concludes, after close scrutiny, that certain criteria are met. See 18 U.S.C. § 208 for more information.

b. prohibit HHS vaccine committee members or HHS employees with duties involving vaccines from accepting any compensation from a vaccine maker for five years?

The current federal ethics laws and regulations do not provide HHS or any other federal agency the authority to restrict the future employment of a career federal employee or an advisory committee member after they leave federal service. However, there are some restrictions on communication by former employees back to their federal agency, such as

a lifetime ban on communicating or appearing before the government on behalf of their new employer or anyone else regarding specific policy matters in which they participated personally and substantially during their entire government service. See 18 U.S.C § 207(a)(1) for more information. There are a number of other exceptions that may apply as well including restrictions on representations to the government for matters under the former employee's official responsibility and restrictions that apply to senior-level government officials.

Federal advisory committee members and career federal employees are prohibited from participating personally and substantially in a particular government matter that will affect their financial interests, as well as the financial interests of their spouse or minor child, general partner, or groups or people covered by 18 U.S.C. § 208. Many federal employees, depending on their duties, must file financial disclosure reports to help identify and mitigate potential conflicts of interest with the employees' duties. See 5 CFR Part 2634. Additionally, special government employees serving on advisory committees must report certain financial interests before attending committee meetings. *See* 5 CFR § 2634.904(a)(2). A 208(b)(3) waiver may be granted to such committee members, based on a determination that the need for the service outweighs the potential for a conflict of interest.

c. require that vaccine safety advocates comprise half of HHS's vaccine committees?

The Vaccine Act defines memberships for the NVAC and ACCV. See 42 U.S.C. §§ 300aa-5 and 300aa-19. The VRBPAC charter states that "Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of immunology, molecular biology, rDNA, virology; bacteriology, epidemiology or biostatistics, vaccine policy, vaccine safety science, federal immunization activities, vaccine development including translational and clinical evaluation programs, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry." You can learn more about the VRBAC charter at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129571.htm. The ACIP charter provides that "the committee shall consist of 15 members, including the Chair. Members and the Chair shall be selected by the Secretary, HHS, from authorities who are knowledgeable in the fields of immunization practices and public health, have expertise in the use of vaccines and other immunobiologic agents in clinical practice or preventive medicine, have expertise with clinical or laboratory vaccine research, or have expertise in assessment of vaccine efficacy and safety. The committee shall include a person or persons knowledgeable about consumer perspectives and/or social and community aspects of immunization programs." You can find out more about the ACIP by reading the charter at

https://www.cdc.gov/vaccines/acip/committee/charter.html. New members are selected based on the candidate's qualifications and their ability to contribute to the specific objectives or needs of the committee, with an overall goal of ensuring a diverse committee that reflects the charge.

d. allocate toward vaccine safety an amount at least equal to 50% of HHS's budget for promoting/purchasing vaccines?

The United States has a robust vaccine safety system that closely and constantly monitors the safety of vaccines. Several agencies within HHS dedicate a significant portion of their budgets and expertise to collaboratively ensure that vaccination efforts are as safe as possible. Due to the significant progress made in the last few years to monitor side effects and conduct relevant vaccine safety research, HHS does not foresee drastically changing current budget allocations in this area. However, this could change pending a vaccine safety signal. Likewise, advances in the development of new vaccines or ways of administering immunizations may require additional vaccine safety funding.

To address comments you made in your letter about vaccine monitoring, I want to clarify a few things. The Vaccine Adverse Event Reporting System (VAERS) is a national system to collect reports of adverse events that happen after vaccination. The adverse events reported to this system are not necessarily caused by vaccination and may or may not be a condition that occurred by chance alone, so they must be further investigated. For more information, please visit: https://vaers.hhs.gov/.

HHS places a priority on vaccine safety. To fulfill public health and regulatory functions, the Centers for Disease Control and Prevention (CDC) and FDA use the Vaccine Safety Datalink (VSD) and Post-licensure Rapid Immunization Safety Monitoring System (PRISM) to evaluate if adverse events are related to vaccination. You can find more details about VSD and PRISM at:
https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html and
http://onlinelibrary.wiley.com/doi/10.1002/pds.2323/abstract.

e. support the creation of a vaccine safety department independent of HHS?

HHS works in close partnership with other federal, state and local agencies, as well as private entities to monitor and communicate about the safety of U.S. vaccines. To adequately address safety-related issues, strengthen the system that monitors the safety of vaccines throughout production and use, and advance the safety profile of vaccines, the expertise of several groups within HHS is required. For example, FDA regulates vaccine clinical trials, licenses vaccines, and monitors vaccine safety after vaccine use and the Health Resources and Services Administration runs the National Vaccine Injury Compensation Program and the Countermeasures Injury Compensation Program. As HHS plays a significant and cross-cutting role in vaccine safety, the diverse federal

vaccine safety portfolio is coordinated at HHS to leverage collaboration among the many groups, inside and outside of HHS, involved in vaccine and immunization activities.

To address your point about conducting research to uncover long-term adverse events, HHS both conducts research in this area and funds outside research in this area. For example, after a safety signal in Europe indicated an increased risk of narcolepsy, a chronic neurological disorder caused by the brain's inability to normally regulate sleep-wake cycles, after vaccination with a monovalent 2009 H1N1 influenza vaccine, CDC began research to determine if there was a safety issue not only in the United States but globally as well. To respond to this signal, an international team of researchers conducted a dynamic retrospective cohort study to estimate incidence rates of narcolepsy diagnoses using a common protocol on electronic data in seven countries during 2003–2013. For the case control study, conducted according to a common protocol in six countries, cases were identified from sleep center records. Overall, the results of this study did not support an association between receipt of the 2009 H1N1 vaccine and narcolepsy. The successful completion of this study proves that the United States has the infrastructure to not only investigate vaccine safety signals at a local level, but to also collaborate with international partners when such signal is of global concern.

f. support the repeal of the 1986 Act to the extent it grants immunity to pharmaceutical companies for injuries caused by their vaccine products?
The National Vaccine Injury Compensation Program (VICP) does vital work to ensure an adequate supply of vaccines, stabilize vaccine costs, and establish and maintain an accessible and efficient forum for individuals found to be injured by certain vaccines. According to the VICP website, over 5000 petitions were compensated, supply shortages of vaccines have been reduced, and pricing of vaccines stabilized since the program was enacted. Likewise, this program provides an alternative to civil litigation that includes attorney fees and costs. Although the Vaccine Act provides liability protections to manufacturers of covered vaccines in many circumstances, these protections are not absolute. The Vaccine Act provides that there are instances when a manufacturer of a covered vaccine is not protected from liability by the Act, such as when an individual files a petition and is requesting damages of $1,000 or less. In such a case, a civil suit against an administrator may be permitted to be filed in state or Federal court without first filing a petition in the VICP.

Further, a repeal of the National Childhood Vaccine Injury Act of 1986 is unlikely. Congress recently passed the 21st Century Cures Act (Public Law 114-255), which made several amendments to the Vaccine Act. The amendments expand the VICP's coverage to include new vaccines that previously were not covered by the VICP (vaccines recommended by the CDC for routine administration in pregnant women) and make clear

that vaccine-injury claims may be filed both with respect to injuries alleged to have been sustained by women receiving covered vaccines during pregnancy and with respect to injuries alleged to have been sustained by live-born children who were in utero at the time those women were administered such vaccines.

Footnote 25

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

JAN 18 2018

Mr. Del Bigtree
Informed Consent Action Network
10200 US HWY 290 W, Suite 301
Austin, Texas 78736

Dear Mr. Bigtree:

Acting Secretary Hargan has asked me to thank you for your letter expressing interest in vaccine safety and in and the federal policies guiding the licensing, recommendation, and safety monitoring of immunizations, and to respond to you directly.

The Department of Health and Human Services has a far-reaching mission to enhance and protect the health of all Americans. Vaccines are held to the highest standard of safety to both protect people from adverse reactions and enhance their health by preventing a number of serious diseases. I am proud to report that data show the United States currently has the safest supply in history.

I have provided responses to your specific questions in the enclosure to this letter. Thank you for the opportunity to address your concerns.

Sincerely yours,

Melinda Wharton

Melinda Wharton, MD, MPH
Acting Director, National Vaccine Program Office

Enclosure

HHS Responses to Questions and Comments from Mr. Bigtree

I would like to address a comment made in section II of your letter about pre-licensure safety review of pediatric vaccines. Contrary to statements made on page two of your letter, many pediatric vaccines have been investigated in clinical trials that included a placebo. In addition, there appears to be a misunderstanding regarding the term "solicited" adverse events. Typically, in vaccine trials, the incidence of certain specific clinical findings that might be expected after vaccination is monitored for a short period of time after vaccination. Because these events are pre-specified, they are considered to be "solicited" events. In addition, other unexpected or severe adverse events, which may occur over a longer period of time following vaccination, are also analyzed and evaluated by FDA, but because these events are not predicted prior to initiation of the study, these are not called "solicited" adverse events. Please be assured that vaccine safety is carefully examined regardless of whether there is a placebo included in the clinical trials. Once vaccines are approved, the safety is also carefully monitored, in some cases by manufacturer-conducted post-marketing studies by Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), or the Post-licensure Rapid Immunization Safety Monitoring System (PRISM), as well as other mechanisms.

(1) Please explain how HHS justifies licensing any pediatric vaccine without first conducting a long-term clinical trial in which the rate of adverse reactions is compared between the subject group and a control group receiving an inert placebo?

Inert placebo controls are not required to understand the safety profile of a new vaccine, and are thus not required. In some cases, inclusion of placebo control groups is considered unethical. Even in the absence of a placebo, control groups can be useful in evaluating whether the incidence of a specific observed adverse event exceeds that which would be expected without administration of the new vaccine. Serious adverse events are always carefully evaluated by FDA to determine potential association with vaccination regardless of their rate of incidence in the control group. In cases where an active control is used, the adverse event profile of that control group is usually known and the findings of the study are reviewed in the context of that knowledge.

(2) Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life?

Data relied upon in licensing infant use of hepatitis B vaccines is summarized in the respective package inserts. Furthermore, pediatric data from other countries and in the literature, support the safety of these vaccines in infants. The recommendation for all children to receive these vaccines was made by the Advisory Committee for

Immunization Practices. Their reasoning is summarized in a *Morbidity and Mortality Weekly Report* at https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm. Follow-up studies support the safety of infant vaccination with hepatitis B vaccines.

(3) Please explain why HHS failed to cooperate with Harvard to automate VAERS reporting? And detail any steps that HHS has taken since toward automating VAERS reporting?

On June 30, 2017, the Centers for Disease Control and Prevention (CDC) and FDA implemented a revised reporting form and a new process for submitting reports to the VAERS for non-manufacturer reports. Persons reporting adverse events are now able to use the VAERS 2.0 online reporting tool to submit reports directly online; alternatively, they may download and complete the writable and savable VAERS 2.0 form and submit it using an electronic document upload feature. Vaccine manufacturers submit VAERS reports electronically through the FDA Electronic Submissions Gateway (ESG). With VAERS 2.0 and the FDA ESG, multiple electronic options exist for VAERS reporting.

In addition, CDC is developing the next generation of spontaneous reporting mechanisms for the VAERS. Following its initial work with Harvard, CDC completed a successful proof of concept study with Harvard and other partners that takes advantage of electronic health records (EHR) and computer algorithms to facilitate direct reporting from EHR systems. You can read about that study at https://academic.oup.com/cid/article/61/6/864/451758. CDC continues to explore options to further develop this capability.

(4) Please explain any specific steps taken by HHS to improve adverse reaction reporting to VAERS?

Please see my response to question #3.

(5) For each of the 38 vaccine-injury pairs reviewed in the 1994 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please refer to the latest review of the "Safety of Vaccines Used for Routine Immunization in the United States" published in 2014 at https://www.ahrq.gov/research/findings/evidence-based-reports/vaccinestp.html. This report reviewed and accepted the findings of the 2011 Institute of Medicine report and provides an independent, systematic review of the literature published after that report on the safety of vaccines recommended for routine immunization of children, adolescents,

and adults in the United States. The report, highlighted in the July 2014 issue of *Pediatrics*, provides the most comprehensive review to date of published studies on the safety of routine vaccines recommended for children in the United States. The report concludes that the risk of rare adverse events must be weighed against the protective benefits that vaccines provide. Furthermore, the Centers for Disease Control and Prevention (CDC) has been working to address several of the vaccine-injury pairs that have been identified in the reports mentioned above. A list of CDC vaccine safety publications can be found at: https://www.cdc.gov/vaccinesafety/research/publications/index.html.

(6) For each of the 135 vaccine-injury pairs reviewed in the 2011 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please see response to question #5.

(7) Please explain what HHS has done to assure that health care providers record the manufacturer and lot number for each vaccine they administer?

Health care providers who administer vaccines covered by the National Vaccine Injury Compensation Program (VICP) are required under the National Childhood Vaccine Injury Act of 1986 (Vaccine Act), as amended, to ensure that the permanent medical record of the recipient (or a permanent office log or file) indicates the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine. This provision of the Vaccine Act applies to any vaccine for which there is a routine recommendation for childhood vaccination, even if many or most doses of the vaccine are administered to adults (e.g., influenza vaccine). In addition, the provider is required to record the edition date of the Vaccine Information Statement (VIS) distributed and the date those materials were provided.

The Advisory Committee on Immunization Practices (ACIP) also issued "General Best Practice Guidelines for Immunization" at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/records.html. This report provides information for clinicians and other health care providers about concerns that commonly arise when vaccinating persons of various ages, and includes a chapter on vaccination records that reinforces the Vaccine Act's requirement to record in the recipient's medical record (or a permanent office log or file) the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine.

(8) Please advise when HHS intends to begin conducting research to identify which children are susceptible to serious vaccine injury? If HHS believes it has commenced this research, please detail its activities regarding same?

HHS is currently supporting several initiatives that focus on advancing research on the fields of precision vaccinology (vaccine formulations tailored on the individual immune reactivity status) and adversomics (the study of vaccine adverse reactions using immunogenomics and systems biology approaches). Two examples are listed below:

- https://www.immuneprofiling.org/hipc/page/showPage?pg=about
- https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

(9) Please confirm that HHS shall forthwith remove the claim that "Vaccines Do Not Cause Autism" from the CDC website, or alternatively, please identify the specific studies on which HHS bases its blanket claim that no vaccines cause autism?

Vaccines are held to strict standards of safety. Many studies have looked at whether there is a relationship between vaccines and autism spectrum disorder (ASD). These studies continue to show that vaccines do **not** cause ASD. For more information, please refer to the literature below:

- https://www.cdc.gov/vaccinesafety/pdf/cdcstudiesonvaccinesandautism.pdf
- http://nationalacademies.org/hmd/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
- http://www.jpeds.com/article/S0022-3476(13)00144-3/pdf?ext=.pdf
  http://nationalacademies.org/HMD/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx

While there is still a lot to learn about ASD, research from public and private organizations indicate that environmental and genetic factors may increase the risk of autism, not vaccines or vaccine ingredients. HHS continues to research this issue to search for answers to better understand the risk factors and causes of this disease. Recent efforts to coordinate autism research are reflected in the "Strategic Plan for Autism Spectrum Disorder Research" by the Interagency Autism Coordinating Committee at https://iacc.hhs.gov/publications/strategic-plan/2017/.

(10) Please advise whether HHS intends to forthwith conduct adequately powered and controlled prospective as well as retrospective studies comparing total health outcomes of fully/partially vaccinated with completely unvaccinated children?

HHS tasked the Institute of Medicine (IOM) to identify research approaches, methodologies, and study designs that could address questions about the safety of the current schedule. This report is the most comprehensive examination of the immunization schedule to date and can be found at http://nationalacademies.org/HMD/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx. The IOM committee uncovered no evidence of major safety concerns associated with adherence to the childhood immunization schedule. The committee also cited ethical concerns about conducting a new study to compare the health outcomes of vaccinated children with their fully unvaccinated counterparts, as this would intentionally leave unvaccinated people and the communities they live in subject to increased risk of death and illness.

Should signals arise that there may be need for investigation, however, the report offers a framework for conducting safety research using existing or new data collection systems. One of the systems that the IOM report considered best suited to conduct these types of studies is CDC's Vaccine Safety Datalink (VSD). In response to the IOM report, CDC commissioned a white paper on the feasibility of conducting studies of the safety of the vaccine schedule in VSD. This report states, "Additionally, CDC has started conducting some of the studies mentioned in the white paper." Additional information on the white paper can be found at: https://www.cdc.gov/vaccinesafety/pdf/whitepapersafety_web.pdf.

(11) Please advise if you will:

a. prohibit conflict waivers for members of HHS's vaccine committees (ACIP, VRBPAC, NVAC & ACCV)?

HHS employs a thorough process for soliciting and vetting candidates for advisory committees to minimize any potential for financial conflicts of interest and works to identify all potential financial conflicts related to the particular matter before a committee. In accordance with 18 U.S.C. § 208(b)(1) and (b)(3), a member of an HHS vaccine advisory committee may be granted a waiver to allow individuals with potentially conflicting financial interests to participate in meetings where it concludes, after close scrutiny, that certain criteria are met. See 18 U.S.C. § 208 for more information.

b. prohibit HHS vaccine committee members or HHS employees with duties involving vaccines from accepting any compensation from a vaccine maker for five years?

The current federal ethics laws and regulations do not provide HHS or any other federal agency the authority to restrict the future employment of a career federal employee or an advisory committee member after they leave federal service. However, there are some restrictions on communication by former employees back to their federal agency, such as

a lifetime ban on communicating or appearing before the government on behalf of their new employer or anyone else regarding specific policy matters in which they participated personally and substantially during their entire government service. See 18 U.S.C § 207(a)(1) for more information. There are a number of other exceptions that may apply as well including restrictions on representations to the government for matters under the former employee's official responsibility and restrictions that apply to senior-level government officials.

Federal advisory committee members and career federal employees are prohibited from participating personally and substantially in a particular government matter that will affect their financial interests, as well as the financial interests of their spouse or minor child, general partner, or groups or people covered by 18 U.S.C. § 208. Many federal employees, depending on their duties, must file financial disclosure reports to help identify and mitigate potential conflicts of interest with the employees' duties. See 5 CFR Part 2634. Additionally, special government employees serving on advisory committees must report certain financial interests before attending committee meetings. *See* 5 CFR § 2634.904(a)(2). A 208(b)(3) waiver may be granted to such committee members, based on a determination that the need for the service outweighs the potential for a conflict of interest.

c. require that vaccine safety advocates comprise half of HHS's vaccine committees?

The Vaccine Act defines memberships for the NVAC and ACCV. See 42 U.S.C. §§ 300aa-5 and 300aa-19. The VRBPAC charter states that "Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of immunology, molecular biology, rDNA, virology; bacteriology, epidemiology or biostatistics, vaccine policy, vaccine safety science, federal immunization activities, vaccine development including translational and clinical evaluation programs, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry." You can learn more about the VRBAC charter at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129571.htm. The ACIP charter provides that "the committee shall consist of 15 members, including the Chair. Members and the Chair shall be selected by the Secretary, HHS, from authorities who are knowledgeable in the fields of immunization practices and public health, have expertise in the use of vaccines and other immunobiologic agents in clinical practice or preventive medicine, have expertise with clinical or laboratory vaccine research, or have expertise in assessment of vaccine efficacy and safety. The committee shall include a person or persons knowledgeable about consumer perspectives and/or social and community aspects of immunization programs." You can find out more about the ACIP by reading the charter at

https://www.cdc.gov/vaccines/acip/committee/charter.html. New members are selected based on the candidate's qualifications and their ability to contribute to the specific objectives or needs of the committee, with an overall goal of ensuring a diverse committee that reflects the charge.

d. allocate toward vaccine safety an amount at least equal to 50% of HHS's budget for promoting/purchasing vaccines?

The United States has a robust vaccine safety system that closely and constantly monitors the safety of vaccines. Several agencies within HHS dedicate a significant portion of their budgets and expertise to collaboratively ensure that vaccination efforts are as safe as possible. Due to the significant progress made in the last few years to monitor side effects and conduct relevant vaccine safety research, HHS does not foresee drastically changing current budget allocations in this area. However, this could change pending a vaccine safety signal. Likewise, advances in the development of new vaccines or ways of administering immunizations may require additional vaccine safety funding.

To address comments you made in your letter about vaccine monitoring, I want to clarify a few things. The Vaccine Adverse Event Reporting System (VAERS) is a national system to collect reports of adverse events that happen after vaccination. The adverse events reported to this system are not necessarily caused by vaccination and may or may not be a condition that occurred by chance alone, so they must be further investigated. For more information, please visit: https://vaers.hhs.gov/.

HHS places a priority on vaccine safety. To fulfill public health and regulatory functions, the Centers for Disease Control and Prevention (CDC) and FDA use the Vaccine Safety Datalink (VSD) and Post-licensure Rapid Immunization Safety Monitoring System (PRISM) to evaluate if adverse events are related to vaccination. You can find more details about VSD and PRISM at:
https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html and
http://onlinelibrary.wiley.com/doi/10.1002/pds.2323/abstract.

e. support the creation of a vaccine safety department independent of HHS?

HHS works in close partnership with other federal, state and local agencies, as well as private entities to monitor and communicate about the safety of U.S. vaccines. To adequately address safety-related issues, strengthen the system that monitors the safety of vaccines throughout production and use, and advance the safety profile of vaccines, the expertise of several groups within HHS is required. For example, FDA regulates vaccine clinical trials, licenses vaccines, and monitors vaccine safety after vaccine use and the Health Resources and Services Administration runs the National Vaccine Injury Compensation Program and the Countermeasures Injury Compensation Program. As HHS plays a significant and cross-cutting role in vaccine safety, the diverse federal

vaccine safety portfolio is coordinated at HHS to leverage collaboration among the many groups, inside and outside of HHS, involved in vaccine and immunization activities.

To address your point about conducting research to uncover long-term adverse events, HHS both conducts research in this area and funds outside research in this area. For example, after a safety signal in Europe indicated an increased risk of narcolepsy, a chronic neurological disorder caused by the brain's inability to normally regulate sleep-wake cycles, after vaccination with a monovalent 2009 H1N1 influenza vaccine, CDC began research to determine if there was a safety issue not only in the United States but globally as well. To respond to this signal, an international team of researchers conducted a dynamic retrospective cohort study to estimate incidence rates of narcolepsy diagnoses using a common protocol on electronic data in seven countries during 2003–2013. For the case control study, conducted according to a common protocol in six countries, cases were identified from sleep center records. Overall, the results of this study did not support an association between receipt of the 2009 H1N1 vaccine and narcolepsy. The successful completion of this study proves that the United States has the infrastructure to not only investigate vaccine safety signals at a local level, but to also collaborate with international partners when such signal is of global concern.

f. support the repeal of the 1986 Act to the extent it grants immunity to pharmaceutical companies for injuries caused by their vaccine products?
The National Vaccine Injury Compensation Program (VICP) does vital work to ensure an adequate supply of vaccines, stabilize vaccine costs, and establish and maintain an accessible and efficient forum for individuals found to be injured by certain vaccines. According to the VICP website, over 5000 petitions were compensated, supply shortages of vaccines have been reduced, and pricing of vaccines stabilized since the program was enacted. Likewise, this program provides an alternative to civil litigation that includes attorney fees and costs. Although the Vaccine Act provides liability protections to manufacturers of covered vaccines in many circumstances, these protections are not absolute. The Vaccine Act provides that there are instances when a manufacturer of a covered vaccine is not protected from liability by the Act, such as when an individual files a petition and is requesting damages of $1,000 or less. In such a case, a civil suit against an administrator may be permitted to be filed in state or Federal court without first filing a petition in the VICP.

Further, a repeal of the National Childhood Vaccine Injury Act of 1986 is unlikely. Congress recently passed the 21st Century Cures Act (Public Law 114-255), which made several amendments to the Vaccine Act. The amendments expand the VICP's coverage to include new vaccines that previously were not covered by the VICP (vaccines recommended by the CDC for routine administration in pregnant women) and make clear

that vaccine-injury claims may be filed both with respect to injuries alleged to have been sustained by women receiving covered vaccines during pregnancy and with respect to injuries alleged to have been sustained by live-born children who were in utero at the time those women were administered such vaccines.

Footnote 26

MMWR

Recommendations and Reports

November 22, 1991 / 40(RR-13);1-19

Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States Through Universal Childhood Vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP)

Immunization Practices Advisory Committee

Membership List, September 1991

CHAIRMAN EX OFFICIO MEMBERS

Samuel L. Katz, M.D. John La Montagne, Ph.D. Duke University Medical Center National Institutes of Health

EXECUTIVE SECRETARY Carolyn Hardegree, M.D.

Food and Drug Administration Claire V. Broome, M.D. Centers for Disease Control LIAISON REPRESENTATIVES

MEMBERS American Academy of Family Physicians

Ronald C. Van Buren, M.D.

- Stanley E. Broadnax, M.D. Columbus, Ohio Cincinnati Health Department

American Academy of Pediatrics

- James D. Cherry, M.D. Georges Peter, M.D. University of California School Providence, Rhode Island

of Medicine (Los Angeles)

Caroline B. Hall, M.D. Mary Lou Clements, M.D. Rochester, New York Johns Hopkins University (Baltimore, Maryland) American College of Physicians

Pierce Gardner, M.D. David W. Fraser, M.D. Stonybrook, New York Swarthmore College (Pennsylvania) American Hospital Association

William Schaffner, M.D.

- Caroline B. Hall, M.D. Nashville, Tennessee University of Rochester

School of Medicine and American Medical Association

Dentistry (New York) Edward A. Mortimer, Jr., M.D.

Cleveland, Ohio Carlos E. Hernandez, M.D. Kentucky Department for Canadian National Advisory Committee

Health Services on Immunization

Susan E. Tamblyn, M.D., Dr. P.H. Gregory R. Istre, M.D. Stratford, Ontario Medical City Hospital Canada (Dallas, Texas)

Department of Defense Carlos H. Ramirez-Ronda, M.D. Michael Peterson, D.V.M. University of Puerto Rico M.P.H., Dr. P.H.

School of Medicine (San Juan) Washington, D.C.

Mary E. Wilson, M.D. National Vaccine Program Mount Auburn Hospital Kenneth J. Bart, M.D. (Cambridge, Massachusetts) Rockville, Maryland

- Terms expired 6/30/91.

The following statement updates all previous recommendations on protection against hepatitis B virus infection, including use of hepatitis B vaccine and hepatitis B immune globulin for prophylaxis against hepatitis B virus infection (MMWR 1985;34:313-24, 329-35, MMWR 1987;36:353-66, and MMWR 1990;39{No. RR-2}:8-19) and universal screening of pregnant women to prevent perinatal hepatitis B virus transmission (MMWR 1988;37:341-46, 51, and MMWR 1990;39{No. RR-2}:8-19). Recommendations concerning the prevention of other types of viral hepatitis are found in MMWR 1990;39(No. RR-2): 1-8, 22-26.

This document provides the rationale for a comprehensive strategy to eliminate transmission of hepatitis B virus in the United States. This prevention strategy includes making hepatitis B vaccine a part of routine vaccination schedules for all infants.

INTRODUCTION

The acute and chronic consequences of hepatitis B virus (HBV) infection are major health problems in the United States. The reported incidence of acute hepatitis B increased by 37% from 1979 to 1989, and an estimated 200,000-300,000 new infections occurred annually during the period 1980- 1991. The estimated 1 million-1.25 million persons with chronic HBV infection in the United States are potentially infectious to others. In addition, many chronically infected persons are at risk of long-term sequelae, such as chronic liver disease and primary hepatocellular carcinoma; each year approximately 4,000-5,000 of these persons die from chronic liver disease (1).

Immunization with hepatitis B vaccine is the most effective means of preventing HBV infection and its consequences. In the United States, most infections occur among adults and adolescents (2,3). The recommended strategy for preventing these infections has been the selective vaccination of persons with

identified risk factors (1,2). However, this strategy has not lowered the incidence of hepatitis B, primarily because vaccinating persons engaged in high-risk behaviors, life-styles, or occupations before they become infected generally has not been feasible. In addition, many infected persons have no identifiable source for their infections and thus cannot be targeted for vaccination (2).

Preventing HBV transmission during early childhood is important because of the high likelihood of chronic HBV infection and chronic liver disease that occurs when children less than 5 years of age become infected (3). Testing to identify pregnant women who are hepatitis B surface antigen (HBsAg)-positive and providing their infants with immunoprophylaxis effec- tively prevents HBV transmission during the perinatal period (4,5). Integrating hepatitis B vaccine into childhood vaccination schedules in populations with high rates of childhood infection (e.g., Alaskan Natives and Pacific Islanders) has been shown to interrupt HBV transmission (6).

This document provides the rationale for a comprehensive strategy to eliminate transmission of HBV and ultimately reduce the incidence of hepatitis B and hepatitis B-associated chronic liver disease in the United States. The recommendations for implementing this strategy include making hepatitis B vaccine a part of routine vaccination schedules for infants.

EPIDEMIOLOGY AND PREVENTION OF HEPATITIS B VIRUS INFECTION

Infections among Infants and Children

In the United States, children become infected with HBV through a variety of means. The risk of perinatal HBV infection among infants born to HBV-infected mothers ranges from 10% to 85%, depending on each mother's hepatitis B e antigen (HBeAg) status (3,7,8). Infants who become infected by perinatal transmission have a 90% risk of chronic infection, and up to 25% will die of chronic liver disease as adults (9). Even when not infected during the perinatal period, children of HBV-infected mothers remain at high risk of acquiring chronic HBV infection by person-to-person (horizontal) transmission during the first 5 years of life (10). More than 90% of these infections can be prevented if HBsAg-positive mothers are identified so that their infants can receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) soon after birth (4,5).

Because screening selected pregnant women for HBsAg has failed to identify a high proportion of HBV-infected mothers (11,12), prenatal HBsAg testing of all pregnant women is now recommended (1,13,14). Universal prenatal testing would identify an estimated 22,000 HBsAg-positive women and could prevent at least 6,000 chronic HBV infections annually (3). Screening and vaccination programs for women and infants receiving care in the public sector have already been initiated through state immunization projects.

Horizontal transmission of HBV during the first 5 years of life occurs frequently in populations in which HBV infection is endemic. The risk of chronic infection is age dependent, ranging from 30% to 60% for children 1-5 years of age (15). Worldwide, it has been recommended that, in popula- tions in which HBV infection is acquired during childhood, hepatitis B vaccine should be integrated into routine vaccination schedules for infants, usually as a part of the World Health Organization's Expanded Programme on Immunization (16). In the United States, racial/ethnic groups shown to have high rates of childhood HBV infection include Alaskan Natives (6,17), Pacific Islanders (18), and infants of first-generation immigrant mothers from parts of the world where HBV infection is endemic, especially Asia (19,20). Vaccination programs to prevent perinatal, childhood, and adult HBV infections among Alaskan Natives were begun in late 1982; as a result, the incidence of acute hepatitis B in this population has declined by over 99% (6). Hepatitis B vaccine was integrated into vaccination schedules for infants in American Samoa beginning in 1986 and by 1990 was incorporated into the schedules of the remaining Pacific Islands under U.S. jurisdiction.

Each year, approximately 150,000 infants are born to women who have immigrated to the United States from areas of the world where HBV infection is highly endemic (3). Children born to HBsAg-positive mothers can be identified through prenatal screening programs. However, children born to HBsAg-

negative immigrant mothers are still at high risk of acquiring HBV infection, usually from other HBV carriers in their families or communities (3,19,20). Infections among these children can be prevented by making hepatitis B vaccine part of their routine infant vaccinations (1).

Infections among Adolescents and Adults

In the United States most persons with hepatitis B acquire the infection as adolescents or adults. Several specific modes of transmission have been identified, including sexual contact, especially among homosexual men and persons with multiple heterosexual partners; parenteral drug use; occupational exposures; household contact with a person who has an acute infection or with a chronic carrier; receipt of certain blood products; and hemodialysis. However, over one-third of patients with acute hepatitis B do not have readily identifiable risk factors (1,2).

The rates of HBV infection differ significantly among various racial and ethnic groups (2,21). For example, the prevalence of infection among adolescents and adults has been shown to be threefold to fourfold greater for blacks than for whites and to be associated with serologic evidence of previous infection with syphilis (21,22).

Efforts to vaccinate persons in the major risk groups have had limited success. For example, programs directed at injecting drug users failed to motivate them to receive three doses of vaccine (CDC, unpublished data). Health-care providers are often not aware of groups at high risk of HBV infection and frequently do not identify candidates for vaccination during routine health-care visits (CDC, unpublished data). In addition, there has been limited vaccination of susceptible household and sexual contacts of HBsAg carriers identified in screening programs for blood donors (23). Hepatitis B vaccination of health-care workers appears to have resulted in a substantial decrease in the rate of disease in this group, but has had little effect on overall rates of hepatitis B (2). Moreover, to achieve widespread vaccination of persons at occupational risk, regulations have had to be developed to ensure implementation of vaccination programs (24).

Educational programs to reduce parenteral drug use and unprotected sexual activity are important components of the strategy to prevent infection with the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome. These programs appear to have reduced the risk of HBV infections among homosexual men but have not had an impact on hepatitis B attributable to parenteral drug use or heterosexual trans- mission (2). Educational efforts alone are not likely to fully eliminate the high-risk behaviors responsible for HBV transmission.

EPIDEMIOLOGY AND PREVENTION OF HEPATITIS DELTA VIRUS INFECTION

Hepatitis delta virus (HDV) is a defective virus that causes infection only in the presence of active HBV infection (25). HDV infection occurs as either coinfection with HBV or superinfection of an HBV carrier. Coinfec- tion usually resolves; superinfection, however, frequently causes chronic HDV infection and chronic active hepatitis. Both types of infection may cause fulminant hepatitis.

Routes of transmission are similar to those of HBV. In the United States, HDV infection most commonly affects persons at high risk of HBV infection, particularly injecting drug users and persons receiving clotting factor concentrates (26). Preventing acute and chronic HBV infection of susceptible persons will also prevent HDV infection.

STRATEGY TO ELIMINATE HEPATITIS B VIRUS TRANSMISSION

A comprehensive strategy to prevent HBV infection, acute hepatitis B, and the sequelae of HBV infection in the United States must eliminate transmission that occurs during infancy and childhood, as well as during adolescence and adulthood. In the United States it has become evident that HBV transmission cannot be prevented through vaccinating only the groups at high risk of infection. No current medical treatment will reliably eliminate chronic HBV infection and thus eliminate the source of new infections in

susceptible persons (27). Therefore, new infections can be prevented only by immunizing susceptible persons with hepatitis B vaccine. Routine visits for prenatal and well-child care can be used to target hepatitis B prevention. A comprehensive prevention strategy includes a) prenatal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for the prevention of perinatal infection and to identify household contacts who should be vaccinated, b) routine vaccin- ation of children born to HBsAg-negative mothers, c) vaccination of certain adolescents, and d) vaccination of adults at high risk of infection.

Infants and children can receive hepatitis B vaccine during routine health-care visits; no additional visits would be required. Costs include that of the vaccine and the incremental expense associated with delivering an additional vaccine during a scheduled health-care visit. Implementation of this immunization strategy would be greatly facilitated by the develop- ment and use of multiple-antigen vaccines (e.g., diphtheria-tetanus- pertussis {DTP}/hepatitis B, Haemophilus influenzae type b conjugate/ hepatitis B). These vaccines would reduce the number of injections received by the infant, reduce the cost of administration, and greatly facilitate widespread vaccine delivery.

Since most HBV infections occur among adults, disease control could be accelerated by vaccinating emerging at-risk populations, such as adoles- cents and susceptible contacts of chronic HBV carriers. The recommendation for universal infant vaccination neither precludes vaccinating adults identified to be at high risk of infection nor alters previous recommen- dations for postexposure prophylaxis for hepatitis B (1).

The reduction in acute hepatitis B and hepatitis B-associated chronic liver disease resulting from universal infant vaccination may not become apparent for a number of years. However, universal HBsAg screening of pregnant women to prevent perinatal HBV infection has been shown to be cost saving (28, CDC, unpublished data), and the estimated cost of universal hepatitis B vaccination for infants is less than the direct medical and work-loss costs associated with the estimated 5% lifetime risk of infection (CDC, unpublished data). Currently, the cost of an infant's dose of hepatitis B vaccine delivered in the public sector is about the same as each of the other childhood vaccinations. Vaccinating adolescents and adults is substantially more expensive because of the higher vaccine cost and the higher implementation costs of delivering vaccine to target populations. In the long term, universal infant vaccination would eliminate the need for vaccinating adolescents and high-risk adults.

PROPHYLAXIS AGAINST HEPATITIS B VIRUS INFECTION

Two types of products are available for prophylaxis against HBV infection. Hepatitis B vaccine, which provides long-term protection against HBV infection, is recommended for both preexposure and postexposure prophylaxis. HBIG provides temporary protection (i.e., 3-6 months) and is indicated only in certain postexposure settings.

Hepatitis B Immune Globulin

HBIG is prepared from plasma known to contain a high titer of antibody against HBsAg (anti-HBs). In the United States, HBIG has an anti-HBs titer of >100,000 by radioimmunoassay. The human plasma from which HBIG is prepared is screened for antibodies to HIV; in addition, the process used to prepare HBIG inactivates and eliminates HIV from the final product. There is no evidence that HIV can be transmitted by HBIG (29,30).

Hepatitis B Vaccine

Two types of hepatitis B vaccine have been licensed in the United States. One, which was manufactured from the plasma of chronically infected persons, is no longer produced in the United States. The currently available vaccines are produced by recombinant DNA technology.

The recombinant vaccines are produced by using HBsAg synthesized by Saccharomyces cerevisiae (common bakers' yeast), into which a plasmid containing the gene for HBsAg has been inserted. Purified HBsAg is obtained by lysing the yeast cells and separating HBsAg from the yeast components by biochemical and biophysical techniques. Hepatitis B vaccines are packaged to contain 10-40 ug of HBsAg protein/mL after adsorption to aluminum hydroxide (0.5 mg/mL); thimerosal (1:20,000 concentration) is added as a preservative.

Routes and sites of administration.

The recommended series of three intramuscular doses of hepatitis B vaccine induces a protective antibody response (anti-HBs >=10 milli-inter- national units {mIU}/mL) in >90% of healthy adults and in >95% of infants, children, and adolescents (31-33). Hepatitis B vaccine should be admin- istered only in the deltoid muscle of adults and children or in the antero- lateral thigh muscle of neonates and infants; the immunogenicity of the vaccine for adults is substantially lower when injections are administered in the buttock (34). When hepatitis B vaccine is administered to infants at the same time as other vaccines, separate sites in the anterolateral thigh may be used for the multiple injections. This method is preferable to administering vaccine at sites such as the buttock or deltoid.

Compared with three standard doses admistered intramuscularly, three low doses of plasma-derived or recombinant vaccine administered intra- dermally to adults result in lower seroconversion rates (55%-81%) and lower final titers of anti-HBs (35-38), although four doses of plasma-derived vaccine administered intradermally have produced responses comparable with vaccine administered intramuscularly (39). Plasma-derived vaccine admin- istered intradermally to infants and children does not induce an adequate antibody response (40). At this time, low-dose intradermal vaccination of adults should be performed only under research protocol with written informed consent. Persons who have been vaccinated intradermally should be tested for anti-HBs. Those with an inadequate response (anti-HBs <10 mIU/ mL) should be revaccinated with three full doses of vaccine administered intramuscularly. Intradermal vaccination should not be used for infants or children.

Vaccination during pregnancy.

On the basis of limited experience, there is no apparent risk of adverse effects to developing fetuses when hepatitis B vaccine is admin- istered to pregnant women (CDC, unpublished data). The vaccine contains noninfectious HBsAg particles and should cause no risk to the fetus. HBV infection affecting a pregnant woman may result in severe disease for the mother and chronic infection for the newborn. Therefore, neither pregnancy nor lactation should be considered a contraindication to vaccination of women.

Vaccine Usage

Preexposure prophylaxis

Vaccination schedule and dose. The vaccination schedule most often used for adults and children has been three intramuscular injections, the second and third administered 1 and 6 months, respectively, after the first. An alternate schedule of four doses has been approved for one vaccine that would allow more rapid induction of immunity. However, for preexposure prophylaxis, there is no clear evidence that this regimen provides greater protection than that obtained with the standard three-dose schedule.

Each vaccine has been evaluated to determine the age-specific dose at which an optimum antibody response is achieved. The recommended dose varies by product and the recipient's age and, for infants, by the mother's HBsAg serologic status (Table_1). In general, the vaccine dose for children and adolescents is 50%-75% lower than that required for adults (Table_1).

Incorporating hepatitis B vaccine into childhood vaccination schedules may require modifications of previously recommended schedules. However, a protective level of anti-HBs (>=10 mIU/mL) was

achieved when hepatitis B vaccine was administered in a variety of schedules, including those in which vaccination was begun soon after birth (5,8,41).

In a three-dose schedule, increasing the interval between the first and second doses of hepatitis B vaccine has little effect on immunogenicity or final antibody titer. The third dose confers optimal protection, acting as a booster dose. Longer intervals between the last two doses (4-12 months) result in higher final titers of anti-HBs (42,43). Several studies have shown that the currently licensed vaccines produce high rates of serocon- version (>95%) and induce adequate levels of anti-HBs when administered to infants at birth, 2 months, and 6 months of age or at 2 months, 4 months, and 6 months of age (CDC, Merck Sharpe & Dohme, SmithKline Beecham, unpub- lished data). When the vaccine is administered in four doses at 0, 1, 2, and 12 months, the last dose is necessary to ensure the highest final antibody titer.

When hepatitis B vaccine has been administered at the same time as other vaccines, no interference with the antibody response of the other vaccines has been demonstrated (44).

If the vaccination series is interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by an interval of at least 2 months. If only the third dose is delayed, it should be administered when convenient.

The immune response when one or two doses of a vaccine produced by one manufacturer are followed by subsequent doses from a different manufacturer has been shown to be comparable with that resulting from a full course of vaccination with a single vaccine.

Larger vaccine doses or an increased number of doses are required to induce protective antibody in a high proportion of hemodialysis patients (45,46) and may also be necessary for other immunocompromised persons (e.g., those who take immunosuppressive drugs or who are HIV positive), although few data are available concerning response to higher doses of vaccine by these patients (47).

Prevaccination testing for susceptibility. Susceptibility testing is not indicated for immunization programs for children or for most adoles- cents because of the low rate of HBV infection and the relatively low cost of vaccine. For adults, the decision to do prevaccination testing should include an analysis of cost effectiveness because of the higher cost of the vaccine. Testing for prior infection should be considered for adults in risk groups with high rates of HBV infection (e.g., injecting drug users, homosexual men, and household contacts of HBV carriers). The decision for testing should be based on whether the costs of testing balance the costs of vaccine saved by not vaccinating already-infected persons. Estimates of the cost effectiveness of testing depend on three variables: the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune persons. If susceptibility testing is being considered, careful attention should also be given to the likelihood of patient follow-up and vaccine delivery.

For routine testing, only one antibody test is necessary (antibody either to the core antigen {anti-HBc} or anti-HBs). Anti-HBc testing identifies all previously infected persons, including HBV carriers, but does not differentiate carriers and non-carriers. The presence of anti-HBs identifies previously infected persons, except for HBV carriers. Neither test has a particular advantage for groups expected to have HBV carrier rates <2%, such as health-care workers. Anti-HBc may be preferable so that unnecessary vaccination of HBV carriers can be avoided in groups with high carrier rates.

Postvaccination testing for serologic response. Such testing is not necessary after routine vaccination of infants, children, or adolescents. Testing for immunity is advised only for persons whose subsequent clinical management depends on knowledge of their immune status (e.g., infants born to HBsAg-positive mothers, dialysis patients and staff, and persons with HIV infection). Postvaccination testing should also be considered for persons at occupational risk who may have exposures from injuries with sharp instruments, because knowledge of their antibody response will aid in determining appropriate postexposure prophylaxis. When necessary, postvac- cination testing should be performed from 1 to 6 months after completion of the vaccine series. Testing after immunoprophylaxis of infants born to

HBsAg-positive mothers should be performed from 3 to 9 months after the completion of the vaccination series (see section on Postexposure prophylaxis).

Revaccination of nonresponders. When persons who do not respond to the primary vaccine series are revaccinated, 15%-25% produce an adequate antibody response after one additional dose and 30%-50% after three additional doses (48). Therefore, revaccination with one or more additional doses should be considered for persons who do not respond to vaccination initially.

Postexposure prophylaxis

After a person has been exposed to HBV, appropriate immunoprophylactic treatment can effectively prevent infection. The mainstay of postexposure immunoprophylaxis is hepatitis B vaccine, but in some settings the addition of HBIG will provide some increase in protection. Table_2 provides a guide to recommended treatment for various HBV exposures.

Transmission of perinatal HBV infection can be effectively prevented if the HBsAg-positive mother is identified and if her infant receives appro- priate immunoprophylaxis. Hepatitis B vaccination and one dose of HBIG, administered within 24 hours after birth, are 85%-95% effective in preventing both HBV infection and the chronic carrier state (4,5,8). Hepatitis B vaccine administered alone in either a three-dose or four-dose schedule (Table_1), beginning within 24 hours after birth, is 70%-95% effective in preventing perinatal HBV infections (8,41). The infants of women admitted for delivery who have not had prenatal HBsAg testing pose problems in clinical management. Initiating hepatitis B vaccination at birth for infants born to these women will provide adequate postexposure prophylaxis if the mothers are indeed HBsAg positive. The few infections not prevented by either of these treatment regimens were most likely acquired in utero or may be due to very high levels of maternal HBV-DNA (49).

Serologic testing of infants who receive immunoprophylaxis to prevent perinatal infection should be considered as an aid in the long-term medical management of the few infants who become HBV carriers. Testing for anti-HBs and HBsAg at 9-15 months of age will determine the success of the therapy and, in the case of failure, will identify HBV carriers or infants who may require revaccination.

Recommendations for postexposure prophylaxis in circumstances other than the perinatal period (Table_2) have been addressed in a previous statement and are reprinted as Appendix A to this document.

Vaccine Efficacy and Booster Doses

Clinical trials of the hepatitis B vaccines licensed in the United States have shown that they are 80%-95% effective in preventing HBV infection and clinical hepatitis among susceptible children and adults (5,33,41,50). If a protective antibody response develops after vaccination, vaccine recipients are virtually 100% protected against clinical illness.

The duration of vaccine-induced immunity has been evaluated in long- term follow-up studies of both adults and children (48,51). Only the plasma-derived hepatitis B vaccine has been evaluated because it has had the longest clinical use; however, on the basis of comparable immunogen- icity and short-term efficacy, similar results would be expected with recombinant vaccines. The magnitude of the antibody response induced by the primary vaccination series is predictive of antibody persistence, and a logarithmic decline of antibody levels occurs over time. Among young adults (homosexual men and Alaskan Eskimos) who initially responded to a three- dose vaccine series, loss of detectable antibody has ranged from 13% to 60% after 9 years of follow-up. For children vaccinated after the first year of life, the rate of antibody decline has been lower than for adults (51). The peak antibody titers for infants are lower than those for children immunized after 12 months of age, but the rate of antibody decline is comparable with that observed for adults in the same population.

Long-term studies of healthy adults and children indicate that immuno- logic memory remains intact for at least 9 years and confers protection against chronic HBV infection, even though anti-HBs levels may

become low or decline below detectable levels (48,51,52). In these studies, the HBV infections were detected by the presence of anti-HBc. No episodes of clinical hepatitis were reported and HBsAg was not detected, although brief episodes of viremia may not have been detected because of infrequent testing. The mild, inapparent infections among persons who have been previously vaccinated should not produce the sequelae associated with chronic HBV infection and should provide lasting immunity. In general, follow-up studies of children vaccinated at birth to prevent perinatal HBV infection have shown that a continued high level of protection from chronic HBV infections persists at least 5 years (52,53).

For children and adults whose immune status is normal, booster doses of vaccine are not recommended, nor is serologic testing to assess antibody levels necessary. The possible need for booster doses will be assessed as additional information becomes available. For hemodialysis patients, vaccine-induced protection may be less complete and may persist only as long as antibody levels are >=10 mIU/mL. For these patients, the need for booster doses should be assessed by annual antibody testing, and a booster dose should be administered when antibody levels decline to <10 mIU/mL.

Vaccine Side Effects and Adverse Reactions

Hepatitis B vaccines have been shown to be safe when administered to both adults and children. Over 4 million adults have been vaccinated in the United States, and at least that many children have received hepatitis B vaccine worldwide.

Vaccine-associated side effects

Pain at the injection site (3%-29%) and a temperature greater than 37.7 C (1%-6%) have been among the most frequently reported side effects among adults and children receiving vaccine (5,31-33,50). In placebo-controlled studies, these side effects were reported no more frequently among vaccinees than among persons receiving a placebo (33,50). Among children receiving both hepatitis B vaccine and DTP vaccine, these mild side effects have been observed no more frequently than among children receiving DTP vaccine alone.

Serious adverse events

In the United States, surveillance of adverse reactions has shown a possible association between Guillain-Barre syndrome (GBS) and receipt of the first dose of plasma-derived hepatitis B vaccine (54, CDC unpublished data). GBS was reported at a very low rate (0.5/100,000 vaccinees), no deaths were reported, and all reported cases were among adults. An estimated 2.5 million adults received one or more doses of recombinant hepatitis B vaccine during the period 1986-1990. Available data from reporting systems for adverse events do not indicate an association between receipt of recombinant vaccine and GBS (CDC, unpublished data).

Until recently, large-scale hepatitis B vaccination programs for infants (e.g., Taiwan, Alaska, and New Zealand) have primarily used plasma- derived hepatitis B vaccine. No association has been found between vaccin- ation and the occurrence of severe adverse events, including seizures and GBS (55, B. McMahon and A. Milne, unpublished data). However, systematic surveillance for adverse reactions has been limited in these populations, and only a small number of children have received recombinant vaccine. Any presumed risk of adverse events possibly associated with hepatitis B vaccination must be balanced against the expected risk of acute and chronic liver disease associated with the current 5% lifetime risk of HBV infection in the United States. It is estimated that, for each U.S. birth cohort, 2,000-5,000 persons will die from HBV-related liver disease.

As hepatitis B vaccine is introduced for routine vaccination of infants, surveillance for vaccine-associated adverse events will continue to be an important part of the program in spite of the current record of safety. Any adverse event suspected to be associated with hepatitis B vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS). VAERS forms can be obtained by calling 1-800-822-7967.

RECOMMENDATIONS

Prevention of Perinatal Hepatitis B Virus Infection

1. All pregnant women should be routinely tested for HBsAg during an early prenatal visit in each pregnancy, preferably at the same time other routine prenatal laboratory testing is done. HBsAg testing should be repeated late in the pregnancy for women who are HBsAg negative but who are at high risk of HBV infection (e.g., injecting drug users, those with intercurrent sexually transmitted diseases) or who have had clinically apparent hepatitis. Tests for other HBV markers are not necessary for the purpose of maternal screening. However, HBsAg- positive women identified during screening may have HBV-related liver disease and should be evaluated (56).

2. Infants born to mothers who are HBsAg positive should receive the appropriate doses of hepatitis B vaccine (Table_1) and HBIG (0.5 mL) within 12 hours of birth. Both should be administered by intra- muscular injection. Hepatitis B vaccine should be administered concur- rently with HBIG but at a different site. Subsequent doses of vaccine should be administered according to the recommended schedule (Table_3).

3. Women admitted for delivery who have not had prenatal HBsAg testing should have blood drawn for testing. While test results are pending, the infant should receive hepatitis B vaccine within 12 hours of birth, in a dose appropriate for infants born to HBsAg-positive mothers (Table_1).

    a. If the mother is later found to be HBsAg positive, her infant should receive the additional protection of HBIG as soon as possible and within 7 days of birth, although the efficacy of HBIG administered after 48 hours of age is not known (57). If HBIG has not been administered, it is important that the infant receive the second dose of hepatitis B vaccine at 1 month and not later than 2 months of age because of the high risk of infection. The last dose should be administered at age 6 months (Table_3). *

    b. If the mother is found to be HBsAg negative, her infant should continue to receive hepatitis B vaccine as part of his or her routine vaccinations (Table_3 and Table_4), in the dose appropriate for infants born to HBsAg-negative mothers (Table_1).

4. In populations in which screening pregnant women for HBsAg is not feasible, all infants should receive their first dose of hepatitis B vaccine within 12 hours of birth, their second dose at 1-2 months of age, and their third dose at 6 months of age as a part of their childhood vaccinations and well-child care (Table_3).

5. Household contacts and sex partners of HBsAg-positive women identified through prenatal screening should be vaccinated. The decision to do prevaccination testing of these contacts to determine susceptibility to HBV infection should be made according to the guidelines in the section "Prevaccination testing for susceptibility." Hepatitis B vaccine should be administered at the age-appropriate dose (Table_1) to those determined to be susceptible or judged likely to be susceptible to infection.

Universal Vaccination of Infants Born to HBsAg-Negative Mothers

1. Hepatitis B vaccination is recommended for all infants, regardless of the HBsAg status of the mother. Hepatitis B vaccine should be incor- porated into vaccination schedules for children. The first dose can be administered during the newborn period, preferably before the infant is discharged from the hospital, but no later than when the infant is 2 months of age (Table_4). Because the highest titers of anti-HBs are achieved when the last two doses of vaccine are spaced at least 4 months apart, schedules that achieve this spacing may be preferable (Table_4). However, schedules with 2-month intervals between doses, which conform to schedules for other childhood vaccines, have been shown to produce a good antibody response (Table_4) and may be appropriate in

populations in which it is difficult to ensure that infants will be brought back for all their vaccinations. The develop- ment of combination vaccines containing HBsAg may lead to other schedules that will allow optimal use of combined antigens.

2. Special efforts should be made to ensure that high levels of hepatitis B vaccination are achieved in populations in which HBV infection occurs at high rates among children (Alaskan Natives, Pacific Islanders, and infants of immigrants from countries in which HBV is endemic).

Vaccination of Adolescents

All adolescents at high risk of infection because they are injecting drug users or have multiple sex partners (more than one partner/6 months) should receive hepatitis B vaccine. Widespread use of hepatitis B vaccine is encouraged. Because risk factors are often not identified directly among adolescents, universal hepatitis B vaccination of teenagers should be implemented in communities where injecting drug use, pregnancy among teenagers, and/or sexually transmitted diseases are common. Adolescents can be vaccinated in school-based clinics, community health centers, family planning clinics, clinics for the treatment of sexually transmitted diseases, and special adolescent clinics.

The 0-, 1-, and 6-month schedule is preferred for vaccinating adoles- cents with the age-appropriate dose of vaccine (Table_1). However, the choice of vaccination schedule should take into account the feasibility of delivering three doses of vaccine over a given period of time. The use of alternate schedules (e.g., 0, 2, and 4 months) may be advisable to achieve complete vaccination.

Vaccination of Selected High-Risk Groups

Efforts to vaccinate persons at high risk of HBV infection should follow the vaccine doses shown in Table_1. High-risk groups for whom vaccination is recommended include:

1. Persons with occupational risk. HBV infection is an occupational hazard for health-care workers and for public-safety workers who have exposure to blood in the workplace (24,58). The risk of acquiring HBV infections from occupational exposures depends on the frequency of percutaneous and permucosal exposure to blood or blood-contaminated body fluids. Any health-care or public-safety worker may be at risk for HBV exposure, depending on the tasks he or she performs. Workers who perform tasks involving contact with blood or blood-contaminated body fluid should be vaccinated (24,58, 59). For public-safety workers whose exposure to blood is infrequent, timely postexposure prophylaxis should be considered rather than routine preexposure vaccination.

   For persons in health-care fields, vaccination should be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions, before trainees have their first contact with blood.

2. Clients and staff of institutions for the developmentally disabled. Susceptible clients in institutions for the developmentally disabled, as well as staff who work closely with clients, should be vaccinated. Susceptible clients and staff who live or work in smaller residential settings with known HBV carriers should also receive hepatitis B vaccine. Clients discharged from residential institutions into community programs should be screened for HBsAg so that appropriate measures can be taken to prevent HBV trans- mission. These measures should include both environmental controls and appropriate use of vaccine.

   Staff of nonresidential day-care programs for the develop- mentally disabled (e.g., schools, sheltered workshops) attended by known HBV carriers have a risk of infection comparable with that of health-care workers and therefore should be vaccinated (60). The risk of infection for other clients appears to be lower than the risk for staff. Vaccination of clients in day care programs may be considered. Vaccination of classroom contacts is strongly encouraged if a classmate who is an

HBV carrier behaves aggres- sively or has special medical problems (e.g., exudative dermatitis, open skin lesions) that increase the risk of exposure to his or her blood or serous secretions.

3. Hemodialysis patients. Hepatitis B vaccination is recommended for susceptible hemodialysis patients. Vaccinating patients early in the course of their renal disease is encouraged because patients with uremia who are vaccinated before they require dialysis are more likely to respond to the vaccine (61). Although their serocon- version rates and anti-HBs titers are lower than those of healthy persons, patients who respond to vaccination will be protected from infection, and the need for frequent serologic testing will be reduced (62).

4. Recipients of certain blood products. Patients who receive clotting-factor concentrates have an increased risk of HBV infection and should be vaccinated as soon as their specific clotting disorder is identified. Prevaccination testing is recom- mended for patients who have already received multiple infusions of these products.

5. Household contacts and sex partners of HBV carriers. All household and sexual contacts of persons identified as HBsAg positive should be vaccinated. The decision to do prevaccination testing to determine susceptibility to HBV infection should be made according to the guidelines described earlier in the section "Prevaccination testing for susceptibility." Hepatitis B vaccine should be admin- istered at the age-appropriate dose (Table_1) to those deter- mined to be susceptible or judged likely to be susceptible to infection.

6. Adoptees from countries where HBV infection is endemic. Adopted or fostered orphans or unaccompanied minors from countries where HBV infection is endemic should be screened for HBsAg (3). If the children are HBsAg positive, other family members should be vaccinated (63).

7. International travelers. Vaccination should be considered for persons who plan to spend more than 6 months in areas with high rates of HBV infection and who will have close contact with the local population. Short-term travelers who are likely to have contact with blood (e.g., in a medical setting) or sexual contact with residents of areas with high or intermediate levels of endemic disease should be vaccinated. Vaccination should begin at least 6 months before travel to allow for completion of the full vaccine series, although a partial series will offer some protection. The alternate four-dose schedule (see Table_1) should provide protection if the first three doses can be delivered before departure.

8. Injecting drug users. All injecting drug users who are susceptible to HBV should be vaccinated as soon as their drug use begins. Because of the high rate of HBV infection in this population, prevaccination screening should be considered as outlined in the section "Prevaccination testing for susceptibility." Injecting drug users known to have HIV infection should be tested for anti-HBs response after completion of the vaccine series. Those who do not respond to vaccination should be counseled accordingly.

9. Sexually active homosexual and bisexual men. Susceptible sexually active homosexual and bisexual men should be vaccinated. Because of the high rate of HBV infection in this population, prevaccination screening should be considered as described in the section "Prevac- cination testing for susceptibility." Men known to have HIV infection should be tested for anti-HBs response after completion of the vaccine series. Those who do not respond to vaccination should be counseled accordingly.

10. Sexually active heterosexual men and women. Vaccination is recom- mended for men and women who are diagnosed as having recently acquired other sexually transmitted diseases, for prostitutes, and for persons who have a history of sexual activity with more than one partner in the previous 6 months (2). Most patients seen in clinics for sexually transmitted diseases should be considered candidates for vaccination.

11. Inmates of long-term correctional facilities. Prison officials should consider undertaking screening and vaccination programs directed at inmates with histories of high-risk behaviors.

EVOLVING ISSUES IN HEPATITIS B IMMUNIZATION PROGRAMS

Hepatitis B vaccine has now been used extensively throughout the world and is currently being incorporated into the Expanded Programme on Immuni- zation of the World Health Organization (16). New information, vaccines, and technology will have implications for this effort, and adjustments and changes are expected to occur over the years. Some of the issues that can be expected to be addressed in clinical and operational studies include the following:

1. In most developing countries with hepatitis B immunization programs, the first dose of vaccine is administered to all infants soon after birth to prevent perinatal infections; pregnant women are not screened for HBsAg; and HBIG is not used (8,16,45). The feasibility and effectiveness of incorporating this approach into the hepatitis B prevention strategy for the United States must be evaluated.

2. Booster doses of hepatitis B vaccine have not been recommended because of the persistence of protective efficacy 9 years after vaccination (48,51). The duration of protective efficacy for adolescents who were vaccinated during infancy or childhood must be evaluated; the results will determine future recommendations concerning booster doses.

3. Flexible dosage schedules are required to effectively integrate hepatitis B vaccine into current and future immunization programs for infants. Schedules may change as optimum dosage and timing are studied and new information becomes available.

4. Multiple-antigen vaccines that incorporate HBsAg as one component are currently being evaluated. The routine use of these vaccines may alter childhood vaccination schedules or may result in the administration of additional doses of certain antigens. However, these vaccines should greatly facilitate vaccine delivery and minimize the number of injections.

References

1. CDC. Protection against viral hepatitis: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1990;39:5-22.

2. Alter MJ, Hadler SC, Margolis HS, et al. The changing epidemiology of hepatitis B in the United States: need for alternative vaccination strategies. JAMA 1990;263:1218-22.

3. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. Semin Liver Dis 1991;11:84-92.

4. Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B virus trans- mission in the United States: prevention by passive-active immuni- zation. JAMA 1985;253:1740-5.

5. Stevens CE, Taylor PE, Tong MJ, et al. Yeast-recombinant hepatitis B vaccine: efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. JAMA 1987;257:2612-6.

6. McMahon BJ, Rhoades ER, Heyward WL, et al. A comprehensive programme to reduce the incidence of hepatitis B virus infection and its sequelae in Alaskan Natives. Lancet 1987;2:1134-6.

7. Stevens CE, Neurath RA, Beasley RP, Szmuness W. HBeAg and anti-HBe detection by radioimmunoassay: correlation with vertical transmission of hepatitis B virus in Taiwan. J Med Virol 1979;3:237-41.

8. Xu Z-Y, Liu C-B, Francis DP, et al. Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. Pediatrics 1985;76:713-8.

9. Beasley RP, Hwang L-Y. Epidemiology of hepatocellular carcinoma. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral hepatitis and liver disease. New York: Grune & Stratton, 1984:209-24.

10. Beasley RP, Hwang L-Y. Postnatal infectivity of hepatitis B surface antigen-carrier mothers. J Infect Dis 1983;147:185-90.

11. Jonas MM, Schiff ER, O'Sullivan MJ, et al. Failure of the Centers for Disease Control criteria to identify hepatitis B infection in a large municipal obstetrical population. Ann Intern Med 1987;107:335-7.

12. Kumar ML, Dawson NV, McCullough AJ, et al. Should all pregnant women be screened for hepatitis B? Ann Intern Med 1987;107:273-7.

13. American Academy of Pediatrics. Hepatitis B. In: Peter G, Lepow ML, McCracken GH, Phillips CF, eds. Report of the Committee on Infectious Diseases. 22nd ed. Elk Grove Village, IL: American Academy of Pedia- trics, 1991:238-55.

14. American Academy of Pediatrics and American College of Obsterics and Gynecology. Guidelines for prenatal care. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics, 1991 (in press).

15. McMahon BJ, Alward WLM, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985;151: 599-603.

16. World Health Organization. Progress in the control of viral hepatitis: memorandum from a WHO meeting. Bull WHO 1988;66:443-55.

17. Schreeder MT, Bender TR, McMahon BJ, et al. Prevalence of hepatitis B in selected Alaskan Eskimo villages. Am J Epidemiol 1983;118:543-9.

18. Wong DC, Purcell RH, Rosen L. Prevalence of antibody to hepatitis A and hepatitis B viruses in selected populations of the South Pacific. Am J Epidemiol 1979;110:227-36.

19. Franks AL, Berg CJ, Kane MA, et al. Hepatitis B virus infection among children born in the United States to Southeast Asian refugees. N Engl J Med 1989;321:1301-5.

20. Hurie MB, Mast EE, Davis JP. Horizontal transmission of hepatitis B virus infection to United States-born children of Hmong refugees. Pediatrics 1992 (in press).

21. McQuillan GM, Townsend TR, Fields HA, et al. The seroepidemiology of hepatitis B virus in the United States, 1976 to 1980. Am J Med 1989;87 (Suppl 3A):5-10.

22. CDC. Racial differences in rates of hepatitis B virus infection -- United States, 1976-1980. MMWR 1989;38:818-21.

23. Moyer LA, Shapiro CN, Shulman G, Brugliera P. A survey of hepatitis B surface antigen positive blood donors: degree of understanding and action taken after notification. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:728-9.

24. US Department of Labor, US Department of Health and Human Services. Joint Advisory Notice. Protection against exposure to hepatitis B virus (HBV) and human immunodeficiency virus (HIV).

Federal Register 1987;52: 41818-24.

25. Rizzetto M. The delta agent. Hepatology 1983;3:729-37.

26. Hadler SC, Fields HA. Hepatitis delta virus. In: Belshe RB, ed. Textbook of human virology. St. Louis: Mosby Year Book, 1991:749-66.

27. Perrillo RP, Schiff ER, Davis FL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. N Engl J Med 1990;323:295-301.

28. Arevalo JA, Washington E. Cost-effectiveness of prenatal screening and immunization for hepatitis B virus. JAMA 1988;259:365-9.

29. CDC. Safety of therapeutic immune globulin preparations with respect to transmission for human T-lymphotrophic virus type III/lymphadenopathy- associated virus infection. MMWR 1986;35:231-3.

30. Wells MA, Wittek AE, Epstein JS, et al. Inactivation and partition of human T-cell lymphotrophic virus, type III, during ethanol fraction- ation of plasma. Transfusion 1986;26:210-3.

31. Zajac BA, West DJ, McAleer WJ, Scolnick EM. Overview of clinical studies with hepatitis B vaccine made by recombinant DNA. J Infect 1986;13(Suppl A):39-45.

32. Andre FE. Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. Am J Med 1989;87(Suppl 3A):14s-20s.

33. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demon- stration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med 1980;303:833-41.

34. Shaw FE Jr, Guess HA, Roets JM, et al. Effect of anatomic injection site, age, and smoking on the immune response to hepatitis B vaccination. Vaccine 1989;7:425-30.

35. Redfield RR, Innis BL, Scott RM, Cannon HG, Bancroft WH. Clinical evaluation of low-dose intradermally administered hepatitis B vaccine, a cost reduction strategy. JAMA 1985;254:3203-6.

36. Coleman PJ, Shaw FE Jr, Serovich J, Hadler SC, Margolis HS. Intradermal hepatitis B vaccination in a large hospital employee population. Vaccine 1991;9:723-7.

37. Gonzalez ML, Usandizaga M, Alomar P, et al. Intradermal and intramus- cular route for vaccination against hepatitis B. Vaccine 1990;8:402-5.

38. Lancaster D, Elam S, Kaiser AB. Immunogenicity of the intradermal route of hepatitis B vaccination with use of recombinant hepatitis B vaccine. Am J Infect Control 1989;17:126-9.

39. King JW, Taylor EM, Crow SD, et al. Comparison of the immunogenicity of hepatitis B vaccine administered intradermally and intramuscularly. Rev Infect Dis 1990;12:1035-43.

40. Xu Z-Y, Margolis HS. Determinants of hepatitis B vaccine efficacy and implications for vaccination strategies. Monogr Virol 1991 (in press).

41. Poovorawan Y, Sanpavat S, Pongpuniert W, Chumdermpadetsuk S, Sentrakul P, Safary A. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. JAMA 1989;261: 3278-81.

42. Jilg W, Schmidt M, Dienhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. J Infect Dis 1989;160:766-9.

43. Hadler SC, Monzon MA, Lugo DR, Perez M. Effect of timing of hepatitis B vaccine dose on response to vaccine in Yucpa Indians. Vaccine 1989;7: 106-10.

44. Coursaget P, Yvonnet B, Relyveld EH, Barres JL, Diop-Mar I, Chiron JP. Simultaneous administration of diphtheria-tetanus-pertussis-polio and hepatitis B vaccines in a simplified immunization program: Immune response to diphtheria toxoid, tetanus toxoid, pertussis and hepatitis B surface antigen. Infect Immun 1986;151:784-7.

45. Stevens CE, Alter HJ, Taylor PE, et al. Hepatitis B vaccine in patients receiving hemodialysis: immunogenicity and efficacy. N Engl J Med 1984; 311:496-501.

46. Jilg W, Schmidt M, Weinel B, et al. Immunogenicity of recombinant hepatitis B vaccine in dialysis patients. J Hepatol 1986;3:190-5.

47. Collier AC, Corey L, Murphy VL, Handsfield HH. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. Ann Intern Med 1988;109:101-5.

48. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 1986; 315:209-14.

49. Lee S-D, Lo K-J, Wu J-C, et al. Prevention of maternal-infant hepatitis B virus transmission by immunization: role of serum hepatitis B virus DNA. Hepatology 1986;6:369-73.

50. Francis DP, Hadler SC, Thompson SE, et al. Prevention of hepatitis B with vaccine: report from the Centers for Disease Control multi-center efficacy trial among homosexual men. Ann Intern Med 1982;97:362-6.

51. Wainwright RB, McMahon BJ, Bulkow LR, et al. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. JAMA 1989;261:2362-6.

52. Lo K-J, Lee S-D, Tsai Y-T, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in infants born to HBeAg-positive HBsAg-carrier mothers. Hepatology 1988;8:1647-50.

53. Hwang L-Y, Lee C-Y, Beasley RP. Five year follow-up of HBV vaccination with plasma-derived vaccine in neonates. Evaluation of immunogenicity and efficacy against perinatal transmission. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:759-61.

54. Shaw FE Jr, Graham DJ, Guess HA, et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination: experience of the first three years. Am J Epidemiol 1988;127:337-52.

55. Chen D-S. Control of hepatitis B in Asia: mass immunization program in Taiwan. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:716-9.

56. CDC. Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues and semen for evidence of hepatitis B and hepatitis C. MMWR 1991;40:5-6.

57. Beasley RP, Hwang L-Y, Stevens CE, et al. Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B virus carrier state: final report of a randomized double-blind, placebo-controlled trial. Hepatology 1983;3:135-41.

58. CDC. Guidelines for prevention of transmission of human immunodefi- ciency virus and hepatitis B virus to health-care and public-safety workers. MMWR 1989;38(Suppl 6):5-15.

59. Department of Labor. Occupational exposure to bloodborne pathogens: proposed rule and notice of hearing. Federal Register 1989;54: 23042-139.

60. Breuer B, Friedman SM, Millner ES, Kane MA, Snyder RH, Maynard JE. Transmission of hepatitis B virus in classroom contacts of mentally retarded carriers. JAMA 1985;254:3190-5.

61. Seaworth B, Drucker J, Starling J, Drucker R, Stevens C, Hamilton J. Hepatitis B vaccines in patients with chronic renal failure before dialysis. J Infect Dis 1988;157:332-7.

62. Moyer LA, Alter MJ, Favero MS. Hemodialysis-associated hepatitis B: revised recommendations for serologic screening. Semin Dialysis 1990;3: 201-4.

63. Hershow RC, Hadler SC, Kane MA. Adoption of children from countries with endemic hepatitis B: transmission risks and medical issues. Pediatr Infect Dis J 1987;6:431-7.

If a four-dose schedule is used (Table_1 and Table_3), the second and third doses should be administered at 1 and 2 months of age, respec- tively, and the fourth dose at 12-18 months of age.

Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 1. Recommended doses of currently licensed hepatitis B vaccines

Group	Recombivax HB * Dose (ug)	(mL)	Engerix-B * Dose (ug)	(mL)
Infants of HBsAg + -negative mothers and children <11 years	2.5	(0.25)	10	(0.5)
Infants of HBsAg-positive mothers; prevention of perinatal infection	5	(0.5)	10	(0.5)
Children and adolescents 11-19 years	5	(0.5)	20	(1.0)
Adults >=20 years	10	(1.0)	20	(1.0)
Dialysis patients and other immunocompromised persons	40	(1.0) &	40	(2.0) @

* Both vaccines are routinely administered in a three-dose series. Engerix-B has also been licensed for a four-dose series administered at 0, 1, 2, and 12 months.
+ HBsAg = Hepatitis B surface antigen.
& Special formulation.
@ Two 1.0-mL doses administered at one site, in a four-dose schedule at 0, 1, 2, and 6 months.

Return to top.

Table_2

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 2. Guide to postexposure immunoprophylaxis for exposure to hepatitis B virus

Type of exposure	Immunoprophylaxis	Reference
Perinatal	Vaccination + HBIG *	p. 11-12
Sexual -- acute infection	HBIG +/- Vaccination	Appendix
Sexual -- chronic carrier	Vaccination	p. 12, 15

Household contact -- chronic carrier	Vaccination	p. 12, 15
Household contact -- acute case	None unless known exposure	Appendix
Household contact -- acute case, known exposure	HBIG +/- vaccination	Appendix
Infant (<12 months) -- acute case in primary care-giver	HBIG + vaccination	Appendix
Inadvertent -- percutaneous/ permucosal	Vaccination +/- HBIG	Appendix

* HBIG = Hepatitis B immune globulin.

Return to top.

Table_3

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 3. Recommended schedule of hepatitis B immunoprophylaxis to prevent perinatal transmission of hepatitis B virus infection

Infant born to mother known to be HBsAg * positive	
Vaccine dose +	Age of infant
First	Birth (within 12 hours)
HBIG &	Birth (within 12 hours)
Second	1 month
Third	6 months @
Infant born to mother not screened for HBsAg	
Vaccine dose **	Age of infant
First	Birth (within 12 hours)
HBIG &	If mother is found to be HBsAg positive, administer dose to infant as soon as possible, not later than 1 week after birth
Second	1-2 months ++
Third	6 months @

* HBsAg = Hepatitis B surface antigen.
+ See Table 1 for appropriate vaccine dose.
& Hepatitis B immune globulin (HBIG) -- 0.5 mL administered intramuscularly at a site different from that used for vaccine.
@ If four-dose schedule (Engerix-B) is used, the third dose is administered at 2 months of age and the fourth dose at 12-18 months.
** First dose = dose for infant of HBsAg-positive mother (see Table 1). If mother is found to be HBsAg positive, continue that dose; if mother is found to be HBsAg negative, use appropriate dose from Table 1.
++ Infants of women who are HBsAg negative can be vaccinated at 2 months of age.

Return to top.

Table_4

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 4. Recommended schedules of hepatitis B vaccination for infants born to HBsAg * -negative mothers

Hepatitis B vaccine	Age of infant
Option 1	
Dose 1	Birth -- before hospital discharge
Dose 2	1-2 months +
Dose 3	6-18 months +
Option 2	
Dose 1	1-2 months +
Dose 2	4 months +
Dose 3	6-18 months +

* HBsAg = Hepatitis B surface antigen.
+ Hepatitis B vaccine can be administered simultaneously with diphtheria-tetanus-pertussis, Haemophilus influenzae type b conjugate, measles-mumps-rubella, and oral polio vaccines at the same visit.

Return to top.

Page converted: 08/05/98

SAFER·HEALTHIER·PEOPLE™
Morbidity and Mortality Weekly Report
Centers for Disease Control and Prevention
1600 Clifton Rd, MailStop E-90, Atlanta, GA 30333, U.S.A

USA.gov Government Made Easy
Department of Health and Human Services

This page last reviewed 5/2/01

Footnote 28

Clinical Trial Ann Intern Med. 1982 Sep;97(3):362-6. doi: 10.7326/0003-4819-97-3-362.

The prevention of hepatitis B with vaccine. Report of the centers for disease control multi-center efficacy trial among homosexual men

D P Francis, S C Hadler, S E Thompson, J E Maynard, D G Ostrow, N Altman, E H Braff, P O'Malley, D Hawkins, F N Judson, K Penley, T Nylund, G Christie, F Meyers, J N Moore Jr, A Gardner, I L Doto, J H Miller, G H Reynolds, B L Murphy, C A Schable, B T Clark, J W Curran, A G Redeker

PMID: 6810736 DOI: 10.7326/0003-4819-97-3-362

Abstract

A randomized, double-blind, vaccine/placebo trial of the Merck 20-micrograms hepatitis B virus (HBV) vaccine was done among 1402 homosexual men attending venereal disease clinics in five American cities. Vaccination was followed by only minimal side effects. Two doses of vaccine induced antibody in 80% of vaccine recipients. A booster dose 6 months after the first dose induced antibody in 85% of recipients and markedly increased the proportion of recipients who produced high antibody titers. The incidence of HBV events was markedly less in the vaccine recipients compared to that in the placebo recipients (p = 0.0004). Between month 3 and 15 after the first dose, 56 more significant HBV events (hepatitis, or hepatitis B surface antigen positive, or both) occurred in the placebo group while only 11 occurred in the vaccine group. Ten of the 11 HBV events in the vaccine recipients occurred in hypo- or nonresponders to the vaccine. This vaccine appears to be safe, immunogenic, and efficacious in preventing infection with hepatitis B virus.

Clinical Trial N Engl J Med. 1980 Oct 9;303(15):833-41. doi: 10.1056/NEJM198010093031501.

Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States

W Szmuness, C E Stevens, E J Harley, E A Zang, W R Oleszko, D C William, R Sadovsky, J M Morrison, A Kellner

PMID: 6997738 DOI: 10.1056/NEJM198010093031501

Abstract

We assessed the efficacy of an inactivated hepatitis B vaccine in a placebo-controlled, randomized, double-blind trial in 1083 homosexual men known to be at high risk for hepatitis B virus infection. The vaccine was found to be safe and the incidence of side effects was low. Within two months, 77% of the vaccinated persons had high levels of antibody against the hepatitis B surface antigen. This rate increased to 96% after the booster dose and remained essentially unchanged for the duration of the trial. For the first 18 months of follow-up, hepatitis B or subclinical infection developed in only 1.4 to 3.4% of the vaccine recipients as compared with 18 to 27% of placebo recipients ($P < 0.0001$). The reduction of incidence in the vaccinees was as high as 92.3%; none of the vaccinees with a detectable immune response to the vaccine had clinical hepatitis B or asymptomatic antigenemia. A significant reduction of incidence was already seen within 75 days after randomization; this observation suggests that the vaccine may be efficacious even when given after exposure.

Related information

Cited in Books
MedGen

LinkOut - more resources

Full Text Sources
Atypon

Other Literature Sources
The Lens - Patent Citations

Medical
ClinicalTrials.gov
Genetic Alliance
MedlinePlus Health Information

Footnote 30

Review Am J Epidemiol. 1988 Feb;127(2):337-52. doi: 10.1093/oxfordjournals.aje.a114808.

Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years

F E Shaw Jr [1], D J Graham, H A Guess, J B Milstien, J M Johnson, G C Schatz, S C Hadler, J N Kuritsky, E E Hiner, D J Bregman, et al.

Affiliations
PMID: 2962488 DOI: 10.1093/oxfordjournals.aje.a114808

Abstract

In 1982, the Centers for Disease Control, the Food and Drug Administration, and the manufacturer created a surveillance system to monitor spontaneous reports of adverse events occurring after inoculation with the new plasma-derived hepatitis B vaccine (Heptavax-B, Merck Sharp and Dohme, West Point, PA). In the three years between June 1, 1982 and May 31, 1985, an estimated 850,000 persons received the vaccine. During that period, a total of 41 reports were received for one of the following neurologic adverse events: convulsions (five cases), Bell's palsy (10 cases), Guillain-Barré syndrome (nine cases), lumbar radiculopathy (five cases), brachial plexus neuropathy (three cases), optic neuritis (five cases), and transverse myelitis (four cases). Half of these occurred after the first of three required vaccine doses. There were no deaths. Calculation of the relative risks of these illnesses after hepatitis B vaccination was highly dependent on diagnostic classification of the cases, estimates of the size of the vaccinated population, background incidence of the diseases, and the length and distribution of the hypothetical at-risk interval used in the analysis. Other factors important in judging the results of the study could not be measured, including underreporting. In some analyses, Guillain-Barré syndrome was reported significantly more often than expected (p less than 0.05, Poisson probability distribution). However, no conclusive epidemiologic association could be made between any neurologic adverse event and the vaccine. Even if such an association did exist, the preventive benefits of the vaccine in persons at high risk for hepatitis B would unequivocally outweigh the risk of any neurologic adverse event.

Genetic Alliance
MedlinePlus Health Information

Footnote 31

JAMA. 1987 May 15;257(19):2612-6. doi: 10.1001/jama.257.19.2612.

Yeast-recombinant hepatitis B vaccine. Efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission

C E Stevens, P E Taylor, M J Tong, P T Toy, G N Vyas, P V Nair, J Y Weissman, S Krugman

PMID: 2952812 DOI: 10.1001/jama.257.19.2612

Abstract

A yeast-recombinant hepatitis B vaccine was licensed recently by the Food and Drug Administration and is now available. To assess the efficacy of the yeast-recombinant vaccine, we administered the vaccine in combination with hepatitis B immune globulin to high-risk newborns. If infants whose mothers were positive for both hepatitis B surface antigen and the e antigen receive no immunoprophylaxis, 70% to 90% become infected with the virus, and almost all become chronic carriers. Among infants in this study who received hepatitis B immune globulin at birth and three 5-micrograms doses of yeast-recombinant hepatitis B vaccine, only 4.8% became chronic carriers, a better than 90% level of protection and a rate that is comparable with that seen with immune globulin and plasma-derived hepatitis B vaccine. These data suggest that, in this high-risk setting, the yeast-recombinant vaccine is as effective as the plasma-derived vaccine in preventing hepatitis B virus infection and the chronic carrier state.

Related information

Cited in Books
MedGen
PubChem Substance

LinkOut - more resources

Full Text Sources
Silverchair Information Systems

Other Literature Sources
The Lens - Patent Citations

Medical
Genetic Alliance
MedlinePlus Health Information

Clinical Trial J Infect. 1986 Jul;13 Suppl A:39-45. doi: 10.1016/s0163-4453(86)92668-x.

Overview of clinical studies with hepatitis B vaccine made by recombinant DNA

B A Zajac, D J West, W J McAleer, E M Scolnick

PMID: 2943814 DOI: 10.1016/s0163-4453(86)92668-x

Abstract

The Merck, Sharp and Dohme hepatitis B vaccine formulated from HBsAg produced by a recombinant strain of Saccharomyces cerevisiae has proven to be highly immunogenic and safe. A 10 micrograms dose of the vaccine produced an anti-HBs response of greater than or equal to 10 IU/l in 91% or more of healthy adults who completed the three-dose regimen. Children responded well to all levels of vaccine antigen utilised but developed maximum anti-HBs titres with 5 micrograms doses. The age of the vaccine recipient affected responsiveness. Younger adults (20-29 years) responded more rapidly and with higher anti-HBs titres than did older adults (greater than or equal to 50 years). Children responded faster and with higher anti-HBs levels than younger adults. Clinical reactions reported after vaccination were mild and transient.

Clinical Trial Am J Med. 1989 Sep 4;87(3A):14S-20S. doi: 10.1016/0002-9343(89)90525-1.

Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine

F E André [1]

Affiliations

PMID: 2528292 DOI: 10.1016/0002-9343(89)90525-1

Abstract

Recombinant deoxyribonucleic acid technology has permitted the development of a vaccine from the hepatitis B surface antigen expressed in genetically manipulated yeast cells. Clinical trials with the vaccine were started in February 1984 and, to date, have involved more than 12,500 persons. The vaccine has been shown to be safe, well tolerated, and immunogenic in healthy persons of all ages and in special target groups likely to require vaccination. The vaccine's protective efficacy has been established in three groups at high risk for hepatitis B infection--homosexual men, institutionalized mentally handicapped patients, and neonates of mothers who are chronic carriers. Production of this vaccine on a large scale should make it less expensive than plasma-derived vaccines and thus broaden the indications for vaccination.

Comment in

You Can Lead a Horse to Water, But Can You Pay to Make Him Drink? An Ethical Analysis of Research on Using Incentives to Promote Patient Health.
Perumalswami P, Branch A, Rhodes R. Perumalswami P, et al. Am J Bioeth. 2016 Oct;16(10):80-2. doi: 10.1080/15265161.2016.1214321. Am J Bioeth. 2016. PMID: 27653415 No abstract available.

Related information

Cited in Books
MedGen

LinkOut - more resources

Full Text Sources
Elsevier Science

Medical
Genetic Alliance
MedlinePlus Health Information

Footnote 34

JAMA. 1987 May 15;257(19):2612-6. doi: 10.1001/jama.257.19.2612.

Yeast-recombinant hepatitis B vaccine. Efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission

C E Stevens, P E Taylor, M J Tong, P T Toy, G N Vyas, P V Nair, J Y Weissman, S Krugman

PMID: 2952812 DOI: 10.1001/jama.257.19.2612

Abstract

A yeast-recombinant hepatitis B vaccine was licensed recently by the Food and Drug Administration and is now available. To assess the efficacy of the yeast-recombinant vaccine, we administered the vaccine in combination with hepatitis B immune globulin to high-risk newborns. If infants whose mothers were positive for both hepatitis B surface antigen and the e antigen receive no immunoprophylaxis, 70% to 90% become infected with the virus, and almost all become chronic carriers. Among infants in this study who received hepatitis B immune globulin at birth and three 5-micrograms doses of yeast-recombinant hepatitis B vaccine, only 4.8% became chronic carriers, a better than 90% level of protection and a rate that is comparable with that seen with immune globulin and plasma-derived hepatitis B vaccine. These data suggest that, in this high-risk setting, the yeast-recombinant vaccine is as effective as the plasma-derived vaccine in preventing hepatitis B virus infection and the chronic carrier state.

Related information

Cited in Books
MedGen
PubChem Substance

LinkOut - more resources

Full Text Sources
Silverchair Information Systems

Other Literature Sources
The Lens - Patent Citations

Medical
Genetic Alliance
MedlinePlus Health Information

Footnote 35

Clinical Trial J Infect. 1986 Jul;13 Suppl A:39-45. doi: 10.1016/s0163-4453(86)92668-x.

Overview of clinical studies with hepatitis B vaccine made by recombinant DNA

B A Zajac, D J West, W J McAleer, E M Scolnick

PMID: 2943814 DOI: 10.1016/s0163-4453(86)92668-x

Abstract

The Merck, Sharp and Dohme hepatitis B vaccine formulated from HBsAg produced by a recombinant strain of Saccharomyces cerevisiae has proven to be highly immunogenic and safe. A 10 micrograms dose of the vaccine produced an anti-HBs response of greater than or equal to 10 IU/l in 91% or more of healthy adults who completed the three-dose regimen. Children responded well to all levels of vaccine antigen utilised but developed maximum anti-HBs titres with 5 micrograms doses. The age of the vaccine recipient affected responsiveness. Younger adults (20-29 years) responded more rapidly and with higher anti-HBs titres than did older adults (greater than or equal to 50 years). Children responded faster and with higher anti-HBs levels than younger adults. Clinical reactions reported after vaccination were mild and transient.

Footnote 37

Clinical Trial Am J Med. 1989 Sep 4;87(3A):14S-20S. doi: 10.1016/0002-9343(89)90525-1.

Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine

F E André [1]

Affiliations

PMID: 2528292 DOI: 10.1016/0002-9343(89)90525-1

Abstract

Recombinant deoxyribonucleic acid technology has permitted the development of a vaccine from the hepatitis B surface antigen expressed in genetically manipulated yeast cells. Clinical trials with the vaccine were started in February 1984 and, to date, have involved more than 12,500 persons. The vaccine has been shown to be safe, well tolerated, and immunogenic in healthy persons of all ages and in special target groups likely to require vaccination. The vaccine's protective efficacy has been established in three groups at high risk for hepatitis B infection--homosexual men, institutionalized mentally handicapped patients, and neonates of mothers who are chronic carriers. Production of this vaccine on a large scale should make it less expensive than plasma-derived vaccines and thus broaden the indications for vaccination.

Comment in

You Can Lead a Horse to Water, But Can You Pay to Make Him Drink? An Ethical Analysis of Research on Using Incentives to Promote Patient Health.
Perumalswami P, Branch A, Rhodes R. Perumalswami P, et al. Am J Bioeth. 2016 Oct;16(10):80-2. doi: 10.1080/15265161.2016.1214321. Am J Bioeth. 2016. PMID: 27653415 No abstract available.

Related information

Cited in Books
MedGen

LinkOut - more resources

Full Text Sources
Elsevier Science

Medical
Genetic Alliance
MedlinePlus Health Information

Footnote 38

USDA

Animal and Plant Health Inspection Service

Veterinary Services

1400 Independence Ave, SW

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.204

TO: Veterinary Services Leadership Team Directors,
Center for Veterinary Biologics Biologics
Licensees, Permittees, and Applicants

FROM: for Jack A. Shere
Deputy Administrator

BURKE HEALEY Digitally signed by BURKE HEALEY Date: 2018.01.25 13:09:42 -05'00'

SUBJECT: General Licensing Considerations: Field Safety Studies

I. PURPOSE

This memorandum provides guidance to applicants for developing target animal field safety data to support an application for a U.S. Veterinary Biological Product License or U.S. Veterinary Biological Product Permit for Distribution and Sale. Regulatory reference can be found in title 9, *Code of Federal Regulations* (9 CFR), parts 102.5 or 104.5, respectively.

II. CANCELLATION

This memorandum cancels Veterinary Services (VS) Memorandum No. 800.204 dated March 16, 2007.

III. BACKGROUND

Licensing considerations provide guidance to applicants concerning the development of data in support of license applications and assist the Center for Veterinary Biologics-Policy, Evaluation, and Licensing (CVB-PEL) in maintaining uniformity and consistency in the review of license applications. General Licensing Considerations address basic principles that have general application in the licensing of products. This document addresses the basic principles for conducting observational field safety trials (FST), which usually satisfy the safety requirements for licensure of biologics administered to healthy animals. More rigorously designed safety studies are sometimes indicated, and they are not covered by this document.

The objective of a typical target animal FST is to assess the safety of the product in its target population under the conditions of its intended use. The goal of the FST is to detect the types of adverse events that may occur with sufficient frequency to be seen in a trial of this scale. The FST is an essential clinical component of the prelicensing process, supplementing smaller preclinical experimental studies, but not replacing ongoing post-marketing surveillance. The FST also may be required to support changes in the recommended administration of licensed products.

IV. GUIDELINES

A. General Requirements. Safety studies must meet the following general requirements:

1. *Permission Required.* All field safety studies must meet the requirements set forth in 9 CFR 103.3 and VS Memorandum No. 800.67. Applicants must obtain permission to conduct a field safety study from the CVB prior to shipping the product to the test sites. See VS Memorandum No. 800.50 for guidance on submitting a field test request to the CVB.

2. *Planning and Execution.* Applicants should plan, execute, and document field safety studies in accordance with the general guidelines provided in VS Memorandum No. 800.200.

B. Experimental Product. Applicants should test more than one serial (numbered lot) of product. The experimental product that applicants use in field safety studies should be produced:

1. *In Accordance With the Filed Outline of Production.* The experimental (prelicense) product the applicant uses for generating field safety data must accurately represent the product that the firm will produce once a product license is granted. The applicant is responsible for establishing the validity of the experimental product used to demonstrate field safety.

2. *In Licensed Production Facilities.* Produce the experimental product in licensed production (not research) facilities, in accordance with filed facility documents.

3. *At, or Above, Release Potency.* The potency of the experimental product should be at, or above, the minimum potency specified in the Outline of Production for serial release.

4. *Largest Combination.* If an applicant has multiple related products (differing only in the number/combination of antigens) being considered for licensure, the applicant should conduct the field safety study with the largest antigen combination. Additional field safety studies are typically not required for fall-out products (i.e., products identical to the tested product except for the removal of one or more antigens) unless specific safety concerns arise.

C. Experimental Protocol. In addition to the general information described in VS Memorandum No. 800.200, field safety study protocols should contain the following specific information:

1. *Study Design.* Field safety studies generally may be satisfied with uncontrolled observational trials of the product under typical field husbandry conditions. The object of such trials is to detect adverse events of unexpected type or frequency that might indicate the need for further investigation.

2. *Geographic Locations.* Applicants should carry out studies in multiple geographic regions. Typically, three distinct regions of the United States are required. When applicable, the applicant should test the product under various conditions of husbandry. Reviewers may use their discretion regarding the acceptability of any proposed combination of sites and must take into account individual circumstances. Reviewers may consider data generated in countries other than the United States, on a case-by-case basis, to fulfill requirements for one of the geographic regions.

3. *Type of Animals.* Applicants should describe the age, breed, sex, pregnancy and/or lactation status, and any other distinguishing features of animals used in the test. All types of animals included in label recommendations should be included in the study.

4. *Number and Age of Animals.* An adequate number of animals of the minimum recommended age should be included in the study. The number of animals may depend on the species and type of animal industry. The minimum age of animals in the safety study should be consistent with the age of animals used in efficacy studies. (If the age of the animals in the efficacy and safety studies is not consistent, the minimum recommended age on labeling will be the older age.) For products intended for use in poultry, production livestock, or aquaculture, all animals in the safety study should be of minimum age. If a product is intended for production livestock species but will be used in animals of breeding age, at least one-third of the animals in the safety study should be of minimum age. Likewise, at least one-third of the animals should be of the minimum age in safety studies of products intended for use in companion animals or horses.

5. *Product Administration.* Test operators should administer the product according to the product label, including the administration of multiple doses and/or alternate routes of administration. Test operators should test each recommended vaccination regimen and each product serial in an equivalent proportion of animals in each geographical region. The protocol should include the number of animals test operators will vaccinate by each regimen and with each serial in each region.

6. *Injection/Administration Sites.* Under select circumstances (e.g., transdermal or ballistic administration, etc.), the CVB may require evaluation of different administration sites (e.g., neck vs. gluteal in large animals, thigh vs. lumbar in companion animals).

7. *Passive vs. Active Immunity.* When a product is recommended for use both in adults and in neonates, for protection of neonates (i.e., has label claims for passive and active immunity), safety must be demonstrated in adults and neonates.

8. *Observation Period.* The protocol should include the frequency and duration of observations, personnel making observations, and the follow-up response to an adverse event. For live products, an acceptable period of observation must take into account the incubation period associated with the live organism(s).

   A qualified investigator (e.g., veterinarian or trained specialist) should actively observe animals in the study at key study points *in addition to* the immediate post-vaccination period. The study protocol should specify the key points.

9. *Reporting Forms.* Provide copies of the reporting form(s) and the instructions that will be issued to field investigators and (if applicable) animal owners. The reporting system must provide for individual animal identification (or group identification for poultry and aquaculture).

10. *Disposal.* The disposal of all animals intended for food used in field safety studies must be in accordance with 9 CFR 103.2.

D. Considerations for Specific Animal Species

1. *Herd animals (mammalian).* For studies where the enrolled animals are maintained post-vaccination in pens or groups:

   a. Test operators should routinely observe animals for adverse events at the intervals specified in the study protocol. It is permissible to conduct these evaluations on a group basis (i.e., do not need to individually handle each animal), provided the group size is small enough to allow adequate observation of each animal within the group.

   b. A qualified investigator should individually examine (including palpation of the injection site) each animal *at least* once after each immediate post-vaccination period. The study protocol should specify the timing of this examination, which should occur when injection site reactions are most likely to be evident. A qualified investigator should continue to examine animals exhibiting palpable injection site reactions at appropriate intervals until the reaction has resolved. The investigator should measure and report the size and duration of all injections site reactions. The investigator should summarize this information in the report and individual studies summary (ISS) and submit it in the electronic data according to CVB Data Guidelines.

2. *Poultry.* When groups are maintained in houses without unique animal identification:

   a. Test operators may use daily mortality sheets as documentation for the FST. The applicants should summarize the information from these sheets in the report and submit it as indicated in section IV.F.5.

b. Test operators generally use comparison houses/farms to evaluate normal mortality rates (formerly referred to as control houses/farms). Acceptable comparisons may utilize data from other houses placed concurrently, data from the same house during the periods immediately before and after placement, historical data from the same house, or other benchmarks used by the poultry company. Historical data should take into account seasonal disease fluctuations. The FST protocol should specify the comparison group.

c. Slaughter data from broilers will only be required on a case-by-case basis. These data may be required if the condemnation lesion is a poultry specific disease characteristic or bears significance to vaccine safety or public health.

d. Daily observation records are required for at least 21 days after vaccination.

e. Studies should compare the typical vaccination regimen of the house/farm site to a regimen with the test vaccine. Therefore, depending on the vaccine, the study could compare vaccination to a lack of vaccination or to vaccination with another product. The report must provide the site's typical vaccination regimen.

f. It is acceptable to use more than three companies or geographical regions or addresses for the FST. A site may include several houses on a farm or several farms for one company. Test operators must include specific farms used in the field safety study in the final field safety study report, but it is not required to identify specific farms in the field safety study protocol. Test operators may use the same region for multiple sites if husbandry differs.

g. It is possible to offer poultry farmers a preliminary trial to evaluate domestic test vaccines with authorization if the test vaccine shares similarities to the firm's licensed products. The preliminary evaluation is considered part of the final FST, though, and test operators must report results. If a small number of birds is included in the preliminary trial, test operators may supplement these results with data generated with additional vaccinated birds.

h. Licensure of niche avian products requires substantially fewer birds than products designed for commercial broiler or layer operations. Examples of niche products include products for pet birds or pigeons.

3. *Aquaculture species*

a. Test operators may use daily mortality sheets as documentation for the FST. Test operators should summarize the information from these sheets in the report and submit it as indicated in section IV.F.5.

b. Test operators may provide information on typical mortality rates from comparison tanks.

c. Applicants may design the study so that they enroll all of the fish of minimum size/age at one site rather than having such fish represented at all sites. Applicants should include and justify the size/age of vaccinated fish in the protocol.

d. Daily observation records are required for 28 days after vaccination to allow time to determine if fish will survive and return to normal feeding habits.

e. If a product is recommended for use in multiple species, applicants must demonstrate field safety in each species.

f. The number of distinct geographical regions is determined by the environmental conditions, which may limit where fish are raised.

g. Licensure requirements of niche products may vary. Examples of niche products may include vaccines for pet fish or public aquariums.

4. *Companion animals.* For studies where each enrolled animal is released to an individual owner after the immediate post-vaccination period, the owners may be given responsibility for certain follow-up observations, provided that:

a. Each owner is provided with a standardized reporting form and instructions for providing feedback (including the absence of adverse events). The investigator should follow up with owners who do not return the reporting form.

b. If the vaccination regimen includes multiple vaccine doses, a qualified investigator should thoroughly evaluate each animal when the animal is presented for each revaccination.

c. If an owner observes an adverse event, he/she should contact the qualified investigator for further guidance. Investigators are encouraged to schedule a follow-up examination of the animal(s) involved in an attempt to describe the adverse event more thoroughly and assess its relationship to the product.

E. Adverse Events

1. *Definition.* An adverse event (AE) is any observation in an animal that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, *whether or not test operators consider it product related.*[1]

1 The definition of AE for field safety studies is found in VS Memorandum No. 800.301 (II. Glossary 1.1).

2. *Types.* AEs may be local or systemic. Test operators should categorize AEs according to standardized low-level terms developed by the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA).[2] The test operators may supplement VeDDRA terms with additional terms to specify further or clarify the AE. See section IV.F.5 for more information.

3. When AEs occur, the test operators should observe the animal until they can assess the duration of the event. Test operators may treat animals experiencing adverse events causing distress to the animal. Test operators should also record the magnitude or severity of the event. Cases of injection site reactions or lymphadenopathy may warrant histopathological evaluation so test operators can define the nature of the reaction.

F. Reporting Requirements

1. *Report All AEs.* Test operators should report all AEs, regardless of the individual making the observation. If a firm wishes to conclude that an event is not related to vaccination, a follow-up evaluation and diagnosis by a veterinarian or trained specialist should be included in the study report. Although it is not always possible to determine a definitive cause for an AE, test operators should attempt to provide objective evidence (e.g., laboratory results) to support the diagnosis.

2. *Necropsy.* Test operators should perform a necropsy on all test animals that die, and the findings must be included in the study report. For poultry and aquatic species, test operators may instead submit daily mortality sheets and slaughter condemnation reports, or the site veterinarian's assessment, although necropsy or diagnostic reports may be necessary to provide additional data regarding unusually high morbidity/mortality. Clearly traumatic deaths, such as hit by a car, do not require necropsies.

3. *Include All Animals.* The disposition of all animals enrolled in the study, including those that do not complete the study and for which follow-up data are unavailable, must be included in the final report.

4. *Presentation of Findings.* Applicants may describe the findings may be described with simple summary statistics set in the relevant context. Trials of this type are usually unsuitable for inferential statistical methods that depend on certain design elements.

5. *Data submission.* To facilitate rapid processing, applicants should submit data as indicated in the CVB Data Guide on the NCAH Portal Guidance web page.

---

[2] Combined VeDDRA list of terms, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC50009480 2.pdf

Footnote 39

CFR - Code of Federal Regulations Title 21

The information on this page is current as of April 1 2019.

For the most up-to-date version of CFR Title 21, go to the Electronic Code of Federal Regulations (eCFR).[6]

[Code of Federal Regulations]
[Title 21, Volume 4]
[Revised as of April 1, 2019]
[CITE: 21CFR201.57]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C--DRUGS: GENERAL

PART 201 -- LABELING

Subpart B--Labeling Requirements for Prescription Drugs and/or Insulin

Sec. 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in 201.56(b)(1).

The requirements in this section apply only to prescription drug products described in 201.56(b)(1) and must be implemented according to the schedule specified in 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) *Highlights of prescribing information.* The following information must appear in all prescription drug labeling:

(1) *Highlights limitation statement.* The verbatim statement "These highlights do not include all the information needed to use (*insert name of drug product*) safely and effectively. See full prescribing information for (insert name of drug product)."

(2) *Drug names, dosage form, route of administration, and controlled substance symbol.* The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by 1302.04 of this chapter.

(3) *Initial U.S. approval.* The verbatim statement "Initial U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the line immediately beneath the established name or, for biological products, proper name of the product.

(4) *Boxed warning.* A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The

summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: "See full prescribing information for complete boxed warning."

(5) *Recent major changes.* A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under 314.70(c)(6) or (d)(2), or 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) *Indications and usage.* A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

(7) *Dosage and administration.* A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

(8) *Dosage forms and strengths.* A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets) and whether the product is scored.

(9) *Contraindications.* A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) *Warnings and precautions.* A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) *Adverse reactions.* (i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA at (*insert current FDA phone number and Web address for voluntary reporting of adverse reactions*)."

(iii) For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions*)."

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) *Drug interactions.* A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(13) *Use in specific populations.* A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) *Patient counseling information statement.* The verbatim statement "See 17 for Patient Counseling Information" or, if the product has FDA-approved patient labeling, the verbatim statement "See 17 for Patient Counseling Information and (insert either FDA-approved patient labeling or Medication Guide)."

(15) *Revision date.* The date of the most recent revision of the labeling, identified as such, placed at the end of Highlights.

(b) *Full prescribing information: Contents.* Contents must contain a list of each heading and subheading required in the full prescribing information under 201.56(d)(1), if not omitted under 201.56(d)(4), preceded by the identifying number required under 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with 201.56(d)(2).

(c) *Full prescribing information.* The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under 201.56(d)(1), unless omitted under 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with 201.56(d)(2).

(1) *Boxed warning.* Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) *1 Indications and usage.* This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint

under 314.510 or 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the "Dosage and Administration" section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in 314.126(b) of this chapter unless this requirement is waived under 201.58 or 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in 314.126(b) of this chapter unless the requirement is waived under 201.58 or 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) *2 Dosage and administration.* (i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

(4) *3 Dosage forms and strengths.* This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) *4 Contraindications.* This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state "None."

(6) *5 Warnings and precautions.* (i) *General.* This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be

taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) *Other special care precautions.* This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

(iii) *Monitoring: Laboratory tests.* This section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) *Interference with laboratory tests.* This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

(7) *6 Adverse reactions.* This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) *Listing of adverse reactions.* This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) *Categorization of adverse reactions.* Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) *Clinical trials experience.* This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped

within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) *Postmarketing experience.* This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) *Comparisons of adverse reactions between drugs.* For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in 314.126(b) of this chapter unless this requirement is waived under 201.58 or 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

(8) *7 Drug interactions.* (i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.

(ii) This section must also contain practical guidance on known interference of the drug with laboratory tests.

(9) *8 Use in specific populations.* This section must contain the following subsections:

(i) *8.1 Pregnancy.* This subsection of the labeling must contain the following information in the following order under the subheadings "Pregnancy Exposure Registry," "Risk Summary," "Clinical Considerations," and "Data":

(A) *Pregnancy exposure registry.* If there is a scientifically acceptable pregnancy exposure registry for the drug, contact information needed to enroll in the registry or to obtain information about the registry must be provided following the statement: "There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (*name of drug*) during pregnancy."

(B) *Risk summary.* The Risk Summary must contain risk statement(s) based on data from all relevant sources (human, animal, and/or pharmacologic) that describe, for the drug, the risk of adverse developmental outcomes (*i.e.,* structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth). When multiple data sources are available, the statements must be presented in the following order: Human, animal, pharmacologic. The source(s) of the data must be stated. The labeling must state the percentage range of live births in the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure. If such information is available for the population(s) for which the drug is labeled, it must also be included. When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary. When applicable, risk statements as described in paragraphs (c)(9)(i)(B)(*1*) and (*2*) of this section must include a cross-reference to

additional details in the relevant portion of the "Data" subheading in the "Pregnancy" subsection of the labeling. If data demonstrate that a drug is not systemically absorbed following a particular route of administration, the Risk Summary must contain only the following statement: "(*Name of drug*) is not absorbed systemically following (route of administration), and maternal use is not expected to result in fetal exposure to the drug."

(*1*) *Risk statement based on human data.* When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the Risk Summary must summarize the specific developmental outcome(s); their incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, this risk must be quantitatively compared to the risk for the same outcome in infants born to women who were not exposed to the drug but who have the disease or condition for which the drug is indicated to be used. When risk information is not available for women with the disease or condition for which the drug is indicated, the risk for the specific outcome must be compared to the rate at which the outcome occurs in the general population. The Risk Summary must state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.

(*2*) *Risk statement based on animal data.* When animal data are available, the Risk Summary must summarize the findings in animals and based on these findings, describe, for the drug, the potential risk of any adverse developmental outcome(s) in humans. This statement must include: The number and type(s) of species affected, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents, and outcomes for pregnant animals and offspring. When animal studies do not meet current standards for nonclinical developmental toxicity studies, the Risk Summary must so state. When there are no animal data, the Risk Summary must so state.

(*3*) *Risk statement based on pharmacology.* When the drug has a well-understood mechanism of action that may result in adverse developmental outcome(s), the Risk Summary must explain the mechanism of action and the potential associated risks.

(C) *Clinical considerations.* Under the subheading "Clinical Considerations," the labeling must provide relevant information, to the extent it is available, under the headings "Disease-associated maternal and/or embryo/fetal risk," "Dose adjustments during pregnancy and the postpartum period," "Maternal adverse reactions," "Fetal/Neonatal adverse reactions," and "Labor or delivery":

(*1*) *Disease-associated maternal and/or embryo/fetal risk.* If there is a serious known or potential risk to the pregnant woman and/or the embryo/fetus associated with the disease or condition for which the drug is indicated to be used, the labeling must describe the risk.

(*2*) *Dose adjustments during pregnancy and the postpartum period.* If there are pharmacokinetic data that support dose adjustment(s) during pregnancy and the postpartum period, a summary of this information must be provided.

(*3*) *Maternal adverse reactions.* If use of the drug is associated with a maternal adverse reaction that is unique to pregnancy or if a known adverse reaction occurs with increased frequency or severity in pregnant women, the labeling must describe the adverse reaction and available intervention(s) for monitoring or mitigating the reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk to the pregnant woman of experiencing the adverse reaction.

(*4*) *Fetal/Neonatal adverse reactions.* If it is known or anticipated that treatment of the pregnant woman increases or may increase the risk of an adverse reaction in the fetus or neonate, the labeling must describe the adverse reaction, the potential severity and reversibility of the adverse reaction, and available intervention(s) for monitoring or mitigating the

reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk.

(*5*) *Labor or delivery.* If the drug is expected to affect labor or delivery, the labeling must provide information about the effect of the drug on the pregnant woman and the fetus or neonate; the effect of the drug on the duration of labor and delivery; any increased risk of adverse reactions, including their potential severity and reversibility; and must provide information about available intervention(s) that can mitigate these effects and/or adverse reactions. The information described under this heading is not required for drugs approved for use only during labor and delivery.

(D) *Data --(1) "Data" subheading.* Under the subheading "Data," the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

(*2*) *Human and animal data headings.* Human and animal data must be presented separately, beneath the headings "Human Data" and "Animal Data," and human data must be presented first.

(*3*) *Description of human data.* For human data, the labeling must describe adverse developmental outcomes, adverse reactions, and other adverse effects. To the extent applicable, the labeling must describe the types of studies or reports, number of subjects and the duration of each study, exposure information, and limitations of the data. Both positive and negative study findings must be included.

(*4*) *Description of animal data.* For animal data, the labeling must describe the following: Types of studies, animal species, dose, duration and timing of exposure, study findings, presence or absence of maternal toxicity, and limitations of the data. Description of maternal and offspring findings must include dose-response and severity of adverse developmental outcomes. Animal doses or exposures must be described in terms of human dose or exposure equivalents and the basis for those calculations must be included.

(ii) *8.2 Lactation.* This subsection of the labeling must contain the following information in the following order under the subheadings "Risk Summary," "Clinical Considerations," and "Data":

(A) *Risk summary.* When relevant human and/or animal lactation data are available, the Risk Summary must include a cross-reference to the "Data" subheading in the "Lactation" subsection of the labeling. When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans. When use of a drug is contraindicated during breastfeeding, this information must be stated first in the Risk Summary.

(*1*) *Drug not absorbed systemically.* If data demonstrate that the drug is not systemically absorbed by the mother, the Risk Summary must contain only the following statement: "(*Name of drug*) is not absorbed systemically by the mother following (route of administration), and breastfeeding is not expected to result in exposure of the child to (*name of drug*)."

(*2*) *Drug absorbed systemically.* If the drug is absorbed systemically, the Risk Summary must describe the following to the extent relevant information is available:

(*i*) *Presence of drug in human milk.* The Risk Summary must state whether the drug and/or its active metabolite(s) are present in human milk. If there are no data to assess this, the Risk Summary must so state. If studies demonstrate that the drug and/or its active metabolite(s) *are* not detectable in human milk, the Risk Summary must state the limits of the assay used. If studies demonstrate the presence of the drug and/or its active metabolite(s) in human milk, the Risk Summary must state the concentration of the drug and/or its active metabolite(s) in human milk and the actual or estimated daily dose for an infant fed exclusively with human milk. The actual or estimated amount of the drug and/or its active

metabolite(s) ingested by the infant must be compared to the labeled infant or pediatric dose, if available, or to the maternal dose. If studies demonstrate the presence of the drug and/or its active metabolite(s) in human milk but the drug and/or its active metabolite(s) are not expected to be systemically bioavailable to the breast-fed child, the Risk Summary must describe the disposition of the drug and/or its active metabolite(s). If only animal lactation data are available, the Risk Summary must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk and specify the animal species.

(*ii*) *Effects of drug on the breast-fed child.* The Risk Summary must include information, on the known or predicted effects on the child from exposure to the drug and/or its active metabolite(s) through human milk or from contact with breast or nipple skin (for topical products). The Risk Summary also must include information on systemic and/or local adverse reactions. If there are no data to assess the effects of the drug and/or its active metabolite(s) on the breast-fed child, the Risk Summary must so state.

(*iii*) *Effects of drug on milk production.* The Risk Summary must describe the effects of the drug and/or its active metabolite(s) on milk production. If there are no data to assess the effects of the drug and/or its active metabolite(s) on milk production, the Risk Summary must so state.

(*3*) *Risk and benefit statement.* For drugs absorbed systemically, unless breastfeeding is contraindicated during drug therapy, the following risk and benefit statement must appear at the end of the Risk Summary: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (*name of drug*) and any potential adverse effects on the breast-fed child from (*name of drug*) or from the underlying maternal condition."

(B) *Clinical considerations.* Under "Clinical Considerations," the following information must be provided to the extent it is available and relevant:

(*1*) *Minimizing exposure.* The labeling must describe ways to minimize exposure in the breast-fed child if: The drug and/or its active metabolite(s) are present in human milk in clinically relevant concentrations; the drug does not have an established safety profile in infants; and the drug is used either intermittently, in single doses, or for short courses of therapy. When applicable, the labeling must also describe ways to minimize a breast-fed child's oral intake of topical drugs applied to the breast or nipple skin.

(*2*) *Monitoring for adverse reactions.* The labeling must describe available intervention(s) for monitoring or mitigating the adverse reaction(s) presented in the Risk Summary.

(C) *Data.* Under the subheading "Data," the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

(iii) *8.3 Females and males of reproductive potential.* When pregnancy testing and/or contraception are required or recommended before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects, this subsection of labeling must contain this information under the subheadings "Pregnancy Testing," "Contraception," and "Infertility," in that order.

(iv) *8.4 Pediatric use.* (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H) of this section, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the "Indications and Usage" section, and appropriate pediatric dosage information must be given under the "Dosage and Administration" section.

The "Pediatric use" subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section. The "Pediatric use" subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(D)(*1*) When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling must contain either the following statement or a reasonable alternative:

The safety and effectiveness of (*drug name*) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (*insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population*).

(*2*) Data summarized in the preceding prescribed statement in this subsection must be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions must be included in the "Dosage and Administration" section. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings and Precautions," and "Dosage and Administration" sections.

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection must contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (__) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(F) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric

subgroups, is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(H) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the "Contraindications" or "Warnings and Precautions" section.

(v) *8.5 Geriatric use.* (A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the "Indications and Usage" section, and appropriate geriatric dosage must be stated under the "Dosage and Administration" section. The "Geriatric use" subsection must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection must be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information must also be contained in the "Warnings and Precautions" and/or "Contraindications" section(s).

(B) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(*1*) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must include the following statement:

Clinical studies of (*name of drug*) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(*2*) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must contain the following statement:

Of the total number of subjects in clinical studies of (*name of drug*), __ percent were 65 and over, while __ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(*3*) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, must refer to more detailed discussions in the "Contraindications," "Warnings and Precautions," "Dosage and Administration," or other sections.

(C)(*1*) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the "Geriatric use" subsection and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" and "Drug Interactions" sections ordinarily contain information on drug/disease and drug/drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

(*2*) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection must include the statement:

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

(D) If use of the drug in the elderly appears to cause a specific hazard, the hazard must be described in the "Geriatric use" subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section, and the "Geriatric use" subsection must refer to those sections.

(E) Labeling under paragraphs (c)(9)(v)(A) through (c)(9)(v)(C) of this section may include statements, if they are necessary for safe and effective use of the drug, and reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (*name of drug*) and observed closely.

(F) If the sponsor believes that none of the requirements described in paragraphs (c)(9)(v)(A) through (c)(9)(v)(E) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative

statement if the agency determines that such statement is accurate and appropriate.

(vi) *Additional subsections.* Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment).

(10) *9 Drug abuse and dependence.* This section must contain the following information, as appropriate:

(i) *9.1 Controlled substance.* If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

(ii) *9.2 Abuse.* This subsection must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used.

(iii) *9.3 Dependence.* This subsection must describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and must identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details must be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state and the principles of treating the effects of abrupt withdrawal must be described.

(11) *10 Overdosage.* This section must be based on human data. If human data are unavailable, appropriate animal and in vitro data may be used. The following specific information must be provided:

(i) Signs, symptoms, and laboratory findings associated with an overdosage of the drug;

(ii) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis);

(iii) Concentrations of the drug in biologic fluids associated with toxicity or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses;

(iv) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life threatening;

(v) Whether the drug is dialyzable; and

(vi) Recommended general treatment procedures and specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be based on data available for the specific drug or experience with pharmacologically related drugs. Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated.

(12) *11 Description.* (i) This section must contain:

(A) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug or, for biological products, the proper name (as defined in 600.3 of this chapter) and any appropriate descriptors;

(B) The type of dosage form(s) and the route(s) of administration to which the labeling applies;

(C) The same qualitative and/or quantitative ingredient information as required under 201.100(b) for drug labels or 610.60 and 610.61 of this chapter for biological product labels;

(D) If the product is sterile, a statement of that fact;

(E) The pharmacological or therapeutic class of the drug;

(F) For drug products other than biological products, the chemical name and structural formula of the drug; and

(G) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(ii) If appropriate, other important chemical or physical information, such as physical constants or pH, must be stated.

(13) *12 Clinical pharmacology.* (i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

(A) *12.1 Mechanism of action.* This subsection must summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (e.g., receptor, membrane, tissue, organ, whole body). If the mechanism of action is not known, this subsection must contain a statement about the lack of information.

(B) *12.2 Pharmacodynamics.* This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity. Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., "Warnings and Precautions" or "Dosage and Administration") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(C) *12.3 Pharmacokinetics.* This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (Cmin), maximum concentration (Cmax), time to maximum concentration (Tmax), area under the curve (AUC), pertinent half-lives (t1/2), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (Vd) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration" or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(ii) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical

studies to be pertinent to clinical use may be included under this section only under the following circumstances:

(A) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(B) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled studies, as defined in 314.126(b) of this chapter, to be necessary for the safe and effective use may be included in this section only if a waiver is granted under 201.58 or 314.126(c) of this chapter.

(14) *13 Nonclinical toxicology.* This section must contain the following subsections as appropriate:

(i) *13.1 Carcinogenesis, mutagenesis, impairment of fertility.* This subsection must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the "Warnings and Precautions" section, must not be included in this subsection of the labeling.

(ii) *13.2 Animal toxicology and/or pharmacology.* Significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling must be included in this section (e.g., specifics about studies used to support approval under 314.600 or 601.90 of this chapter, the absence of chronic animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

(15) *14 Clinical studies.* This section must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required under 201.56 and 201.57 because the study is essential to an understandable presentation of the information in that section of the labeling, any detailed discussion of the study must appear in this section.

(i) For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in 314.126(b) of this chapter and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section. For biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section.

(ii) Any discussion of a clinical study that relates to a risk from the use of the drug must also refer to the other sections of the labeling where the risk is identified or discussed.

(16) *15 References.* When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(17) *16 How supplied/storage and handling.* This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must include, as appropriate:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets) and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation;

(ii) The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100);

(iii) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number; and

(iv) Special handling and storage conditions.

(18) *17 Patient counseling information.* This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling. Any FDA-approved patient labeling printed immediately following this section or accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be detached and distributed to patients in compliance with 208.24 of this chapter. Medication Guides for distribution to patients are subject to the type size requirements set forth in 208.20 of this chapter.

(d) *Format requirements.* All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2-inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

[71 FR 3988, Jan. 24, 2006, as amended at 79 FR 72101, Dec. 4, 2014]

Links on this page:

1. http://www.addthis.com/bookmark.php?u508=true&v=152&username=fdamain
2. http://www.addthis.com/bookmark.php
3. https://www.fda.gov/
4. https://www.fda.gov/MedicalDevices/default.htm
5. https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm
6. https://www.ecfr.gov/cgi-bin/ECFR?page=browse
7. /scripts/cdrh/cfdocs/search/default.cfm?FAQ=true
8. https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/ucm135680.htm

Footnote 43

ICAN
Informed Consent Action Network

March 12, 2020

U.S. Department of Health & Human Services
HHS Office of the Secretary
Alex M. Azar II, Secretary of Health & Human Services
Tammy R. Beckham, Acting Director, National Vaccine Program Office
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *HHS Vaccine Safety Responsibilities and Notice Pursuant to 42 U.S.C. § 300aa-31*

Dear Secretary Azar:

In our letter of October 12, 2017, we notified the Department of Health & Human Services (**HHS**) about a number of serious concerns regarding how HHS fulfills its obligations to ensure vaccine safety under the National Childhood Vaccine Injury Act of 1986 (the **1986 Act**).[1] We voiced these concerns along with 55 other organizations who were copied on our letter and who represent over 5 million Americans.[2]

HHS responded to our letter in a reply dated January 18, 2018. That letter was reviewed and cleared by the following agencies within HHS: the Centers for Disease Control and Prevention (**CDC**), the Food & Drug Administration (**FDA**), the National Institutes of Health (**NIH**), the Office of the General Counsel (**OGC**), the Human Resources & Services Administration (**HRSA**), and the Agency for Healthcare Research and Quality (**AHRQ**).[3]

After carefully reviewing the extensive information provided in HHS's reply, ICAN responded by letter dated December 31, 2018.[4] ICAN provided detailed information, mostly from HHS's own primary sources, as to why HHS's reply of January 18, 2018 either did not address or heightened the serious concerns raised in ICAN's prior letter. In that regard, we submitted a number of follow-up questions in Appendix A to that letter.

[1] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[2] http://icandecide.org/hhs/vaccine-safety-10-12-17.pdf
[3] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf
[4] https://icandecide.org/hhs/vaccines-safety-12-31-18.pdf

It has now been over 13 months since ICAN submitted these follow-up questions and concerns regarding vaccine safety. Nonetheless, HHS has failed to respond to the questions posed in our letter of December 31, 2018, nor to any of the substance in that letter.

HHS's failure and/or apparent inability to respond to ICAN's simple vaccine safety questions and concerns provides further support that the Secretary of HHS has failed to fulfill his vaccine safety obligations pursuant to the 1986 Act.

Absent a substantive response to the questions and substance of our December 31, 2018letter within sixty days of this notice, an action against the Secretary of HHS shall be filed pursuant to 42 U.S.C. § 300aa-31.

For your convenience, copies of the three prior letters are enclosed herein.

ICAN reserves all rights. Govern yourself accordingly.

Very truly yours,

Del Bigtree
President

Enclosures

Footnote 44

SIRI & GLIMSTAD LLP

200 PARK AVENUE
SEVENTEENTH FLOOR
NEW YORK, NY 10166
P: (212) 532-1091
F: (646) 417-5967
WWW.SIRILLP.COM

FREEDOM OF INFORMATION ACT REQUEST

VIA EMAIL June 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of the Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

Re: FDA Reports Used in Approving Engerix-B in 1989 (IR#0133)

Dear Sir or Madam:

This firm represents Informed Consent Action Network ("ICAN"). On behalf of ICAN, we hereby request records pursuant to the Freedom of Information Act (5 U.S.C. § 552, as amended) from the files of the Food and Drug Administration ("FDA").

Please provide the following records in FDA's possession to alucas@sirillp.com in electronic form:

> **A copy of the report for each clinical trial relied upon by the FDA to approve Engerix-B for babies and children in 1989 that had a safety review period longer than seven days following administration of this vaccine.**

We ask that you waive any and all fees or charges pursuant to 5 U.S.C. § 552 (a)(4)(A)(iii). ICAN is a not-for-profit 501(c)(3) organization whose mission is to raise public awareness about vaccine safety and to provide the public with information to give informed consent. As part of their mission, ICAN actively investigates and disseminates information regarding vaccine safety issues, including through their website, and through press events and releases. They are seeking the information in this FOIA request to allow them to contribute to the public understanding of the government's vaccine safety programs, including the government's efforts to promote vaccine safety. The information we are requesting will not contribute to any commercial activities.

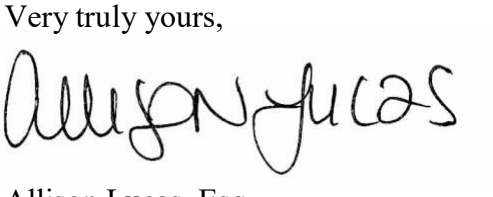
Please note that the FOIA provides that if only portions of a requested file are exempted from release, the remainder must still be released. We therefore request that we be provided with all non-exempt portions which are reasonably segregable. We further request that you describe

any deleted or withheld material in detail and specify the statutory basis for the denial as well as your reasons for believing that the alleged statutory justification applies. Please also separately state your reasons for not invoking your discretionary powers to release the requested documents in the public interest. Such statements may help to avoid unnecessary appeal and litigation. ICAN of course reserves all rights to appeal the withholding or deletion of any information.

Access to the requested records should be granted within twenty (20) business days from the date of your receipt of this letter. Failure to respond in a timely manner shall be viewed as a denial of this request and ICAN may immediately file an administrative appeal.

If you would like to discuss our requests or any issues raised in this letter, please feel free to contact me at (212) 532-1091 during business hours or email me at alucas@sirillp.com. Thank you for your time and attention to this matter.

Very truly yours,



Allison Lucas, Esq.
Licensed in MI

SIRI & GLIMSTAD LLP

200 PARK AVENUE
SEVENTEENTH FLOOR
NEW YORK, NY 10166
P: (212) 532-1091
F: (646) 417-5967
WWW.SIRILLP.COM

FREEDOM OF INFORMATION ACT REQUEST

VIA EMAIL June 7, 2019

Food and Drug Administration
Division of Freedom of Information
Office of the Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

Re: FDA Reports Regarding Recombivax HB in 1986 (IR#0125)

Dear Sir or Madam:

This firm represents Informed Consent Action Network ("ICAN"). On behalf of ICAN, we are requesting records pursuant to the Freedom of Information Act (5 U.S.C. § 552, as amended) from the files of the Food and Drug Administration ("FDA").

By this letter, please provide the following records in FDA's possession to the above referenced address in electronic form via email to alucas@sirillp.com:

> **A copy of the report for each clinical trial relied upon by the FDA to approve Recombivax HB for babies and children in 1986 that had a safety review period longer than seven days following administration of this vaccine.**

We ask that you waive any and all fees or charges pursuant to 5 U.S.C. § 552 (a)(4)(A)(iii). ICAN is a not-for-profit 501(c)(3) organization whose mission is to raise public awareness about vaccine safety and to provide the public with information to give informed consent. As part of their mission, ICAN actively investigates and disseminates information regarding vaccine safety issues, including through their website, and through press events and releases. They are seeking the information in this FOIA request to allow them to contribute to the public understanding of the government's vaccine safety programs, including the government's efforts to promote vaccine safety. The information we are requesting will not contribute to any commercial activities.

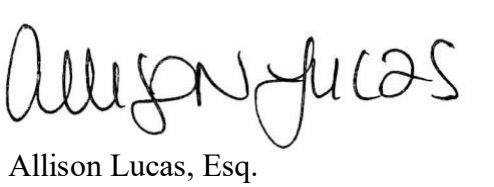
Please note that the FOIA provides that if only portions of a requested file are exempted from release, the remainder must still be released. We therefore request that we be provided with all non-exempt portions which are reasonably segregable. We further request that you describe any deleted or withheld material in detail and specify the statutory basis for the denial as well as your reasons for believing that the alleged statutory justification applies. Please also separately

state your reasons for not invoking your discretionary powers to release the requested documents in the public interest. Such statements may help to avoid unnecessary appeal and litigation. ICAN of course reserves all rights to appeal the withholding or deletion of any information.

Access to the requested records should be granted within twenty (20) business days from the date of your receipt of this letter. Failure to respond in a timely manner shall be viewed as a denial of this request and ICAN may immediately file an administrative appeal.

If you would like to discuss our requests or any issues raised in this letter, please feel free to contact me at (212) 532-1091 or alucas@sirillp.com during normal business hours. Thank you for your time and attention to this matter.

Very truly yours,



Allison Lucas, Esq.
Licensed in MI