

**UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK**

INFORMED CONSENT ACTION NETWORK,

Plaintiff,

-against-

UNITED STATES FOOD AND DRUG  
ADMINISTRATION,

Defendant.

1:20-cv-00689-AJN

**MEMORANDUM OF LAW IN FURTHER SUPPORT OF  
PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT**

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Plaintiff Informed Consent Action Network (“**ICAN**” or “**Plaintiff**”), submits this memorandum of law in further support of its cross-motion for summary judgment.

### **PRELIMINARY STATEMENT**

The parties agree, the principal question in this matter is whether Plaintiff’s request “reasonably describes” the records sought. The parties’ papers show it does. Any argument that the United States Food and Drug Administration (“**FDA**” or “**Defendant**”) does not understand the term “safety review period” in regard to clinical trials is not credible.

Prior to licensure, the FDA reviewed the clinical trials for Engerix-B, like every other vaccine, in order to determine whether the product was safe. As with any vaccine, the protocol of each of those clinical trials specifies the duration it reviewed the product for safety. ICAN is merely requesting a copy of any of the clinical trials relied upon by the FDA to license Engerix-B whose protocol provided for reviewing safety for any period exceeding seven days – a straightforward and reasonable request.

Any individual can go to the website [clinicaltrials.gov](https://www.clinicaltrials.gov), review a trial summary, and deduce what the safety duration was – these safety periods are explicitly stated in the “Outcome Measures” section. For example, the clinical trial that will be relied upon to license Pfizer’s COVID-19 vaccine states in its protocol: “Percentage of participants in Phase 2/3 reporting serious adverse events [Time Frame: From dose 1 through 6 months after the last dose].”<sup>1</sup> From this, one can determine that safety is reviewed for 6 months for serious adverse events. If the instant request was made for Pfizer’s COVID-19 vaccine, this clinical trial would be responsive. Engerix-B however, was licensed before trial summaries were published on clinicaltrials.gov.

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<sup>1</sup><https://www.clinicaltrials.gov/ct2/show/NCT04368728> (last visited September 20, 2020).

In objecting to ICAN's clear request, the FDA attempts to cast ICAN as obstructionist in failing to cooperate to assist it in understanding the request. Nothing could be further from the truth. As reiterated to the FDA prior to and during this action, ICAN merely seeks the clinical trials the FDA relied upon to license Engerix-B for babies and children that reviewed safety for more than seven days after each administration of the product. Surely, the FDA knows how long safety was reviewed in the clinical trials on which it relied. The FDA's claim that it requires "clairvoyant capabilities" to determine how long safety was reviewed simply cannot be true.

ICAN requested targeted clinical trials, as opposed to the full set of clinical trials. As Burk's Declaration shows, ICAN previously made 9 requests for all clinical trials for other products. On average, it took over a full year for the FDA to produce these reports. The FDA now faults ICAN for making a more precise request.

ICAN's request is definite and ascertainable. The FDA's defense is to set up a straw man by rewriting that request and presenting bad faith arguments in the process. For reasons set forth in ICAN's opening brief and herein, the FDA should be ordered to respond to the FOIA request.

## **ARGUMENT**

### **I. THE FOIA REQUEST REASONABLY DESCRIBES THE CLINICAL TRIALS SOUGHT**

#### **A. The Request is Precise and the Phrase "Safety Review Period Longer Than Seven Days After Administration" is Definite, Specific, and Ascertainable**

The FDA objected to ICAN's FOIA request asserting that it did not reasonably describe the clinical trials Plaintiff sought because the FDA cannot identify the trials that reviewed safety for more than seven days. This objection is not credible. First, the FDA's *raison d'être* with regard to vaccines, such as Engerix-B, is to review clinical trials to determine whether vaccines are safe and effective. The very first sentence of the FDA's webpage for "Vaccines" states: "Vaccines... undergo a *rigorous review of laboratory and clinical data* to ensure the safety...of

these products.”<sup>2</sup> It is, as the FDA explains, “What We Do.” Second, the actual wording of the request is clear: (i) to anyone familiar with clinical trials, it is obvious that a safety review period would be the period the trial’s protocol provides that safety is to be reviewed during the trial; and (ii) “following administration” clearly means after receiving each dose of the vaccine. Therefore, if the trial protocol provided that adverse events were to be reported for more than seven days after the administration of any dose of Engerix-B, those clinical trials would be responsive to ICAN’s request.

The FDA would have this Court believe it is incapable of determining the safety review period in clinical trials of a product it licensed for injection into every newborn in this country. That position is not credible. Indeed, after claiming it could not understand the words “safety review period” in its opening brief, Plaintiff provided examples in its opposition where the FDA used that precise term. Given this, the FDA conceded in its reply that “the phrase ‘safety review period’ has been used, in context, in a few FDA documents regarding drug trials.” (Dkt. No. 19 at 4).

The clinical trial reports previously produced to ICAN for other vaccines, enumerated in Burk’s declaration, make plain that identifying which clinical trials reviewed safety for more than seven days is not hard. A quick review of the clinical trial reports of the MMR-II vaccine, licensed in 1978, shows it reviewed safety for 42 days after administration. *See Exhibit A.*<sup>3</sup> For IPOL, licensed in 1990, one trial location reviewed safety for up to 3 days after administration, and another location only inquired about in an interview during the administration visit (*see Exhibit B*); and PedVaxHIB, licensed in 1989, the same year as Engerix-B, followed safety for 5 days post-vaccination and 14 days post-vaccination for serious adverse events (*see Exhibit C*).

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<sup>2</sup> <https://www.fda.gov/vaccines-blood-biologics/vaccines> (last visited September 11, 2020).

<sup>3</sup> All Exhibits referenced herein are attached to this Reply and include excerpts of the relevant pages of each trial.

## **B. The FDA Misrepresents the Recombivax Clinical Trial Reports**

It is telling that the FDA used the clinical trial for Recombivax, another Hepatitis B vaccine, in its Reply to feign confusion and to distract the Court, instead of presenting the Court with the Engerix-B records at issue. In pointing to Recombivax, the FDA's representation of those documents is a clear example of bad faith.<sup>4</sup> The FDA did not disclose to the Court the pages from each clinical trial for Recombivax that expressly provide the period that safety was reviewed pursuant to the protocol for each trial. There were 3 clinical trials conducted on healthy children. In each instance, the trial provided for 5 days of safety review, clearly stated on the second page of the trial in the "Procedure" section. Attached as **Exhibit D** are the relevant pages that the FDA failed to disclose to this Court in its Reply and Supplemental Declaration (Dkt. Nos. 19 and 20).

In fact, not only is the duration of the safety review listed in the "Procedure" section of each clinical trial for Recombivax, but the FDA's own 9-page "Summary of Basis Approval" for Recombivax clearly states: "Vaccine recipients were asked to report their temperature and any injection site or systemic complaints that occurred within a five-day period following each injection of vaccine." **Exhibit E.** The FDA's claim that it cannot discern the duration that safety was reviewed in the protocol for Recombivax is dumbfounding given that it is written in black-and-white in each trial.

The lack of effort required to determine the period safety was reviewed in Recombivax's clinical trials shows that the FDA's representations regarding this trial were false and plainly made in bad faith. The FDA is certainly able to determine the period safety is reviewed in the clinical

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<sup>4</sup> In addition, Burk's Declaration (Dkt. No. 20) further misleads the Court in its non-chronological re-telling of ICAN's Recombivax requests. ICAN's first request for Recombivax clinical trials was made in August 2018. Ten months later, in June 2019, when no significant production had been made, ICAN submitted a new, narrowly tailored request seeking only the clinical trials for which safety had been reviewed for longer than seven days in the hopes of focusing the FDA and actually receiving the documents it was most interested in. Only 5 months later, in November 2019, did the FDA produce records responsive to the original August 2018 request.

trials for Engerix-B, as was easily done with Recombivax, and can produce only those clinical trials it relied upon to license Engerix-B that included a protocol for reviewing safety for more than a week, or advise that it has nothing responsive to this request if that is the case.

### **C. FDA Pretends it Cannot Review a Clinical Trial Report**

The FDA's declarations from Ms. Burk describe a "disclosure reviewer processing FOIA requests" as the individual tasked with determining whether or not documents are responsive to ICAN's request. (Dkt. No. 16 at 6). The FDA is required to have "a professional employee of the agency familiar with the subject matter" review for responsive records and it is not clear that the FDA has complied with this requirement. *Freedom Watch, Inc. v. CIA*, CV No. 12-0721, 895 F. Supp. 2d 221, 2012 U.S. Dist. (D.D.C. 2012). An agency employee familiar with the subject matter – clinical trials and licensing – should reasonably be able to determine for how long safety was tracked. The FDA cannot, in good faith, assign this duty to a "disclosure reviewer" with no knowledge of clinical trials and then use that reviewer's ignorance of agency responsibilities to place blame on the requester and avoid disclosure.

ICAN's duty is to reasonably describe the records sought, which it has done; and the FDA's duty is to then have "a professional employee of the agency familiar with the subject matter" determine which records are responsive. The FDA's declarations, therefore, are insufficient to support a finding that its search was adequately undertaken by the appropriate employee. *See Judicial Watch*, 2016 U.S. Dist. LEXIS 200935, at \*8 ("...discovery may be granted when ... a factual dispute exists and the plaintiff has called the affidavits submitted by the government into question."); *see also Landmark Legal Found. v. EPA*, 959 F. Supp. 2d 175 (D.D.C. 2013) (permitting discovery where issues of fact precluded summary judgment and it was possible the agency deliberately misinterpreted the scope of the FOIA request).



The FOIA request seeks a simple set of documents. If the FDA has nothing responsive to the request, that is an appropriate response. The FDA implies that ICAN has designed its FOIA request “as a trap” and cites to *Hall & Assocs.* which prohibits such a “trap” where the agency must “either...produce[] or create[s] documents disproving [the requester’s] accusations, or the [requester] would assume based on the lack of response that [the agency] could not disprove them.” That case examined requests that required the agency to make a judgment as to whether a document showed a stated allegation was false. Here, there is no such accusation or conclusion levied by ICAN, instead the FOIA request seeks specific documents that objectively exist or do not exist.

It appears from the FDA’s reply brief that its real objection is that it does not want to admit that either (i) there are no such clinical trials; or (ii) it does not know how long safety was reviewed in these trials, and instead, would rather litigate this simple request. This bad faith conduct and the semantical, hair-splitting, tongue twisting arguments the FDA presents are a waste of judicial and party resources – the very essence of bad faith. *Judicial Watch v. United States Dep’t of State*, No. 13-1363, 2016 U.S. Dist. LEXIS 200935, at \*8 (D.D.C. 2016) (“...discovery may be granted when plaintiff has made a sufficient showing that the agency acted in bad faith..., has raised a sufficient question as to the agency’s good faith..., or when a factual dispute exists and the plaintiff has called the affidavits submitted by the government into question.”) *see also* U.S. Dep’t of Justice, Guide to the Freedom of Information Act 812 (2009 Ed.) (“The major exception to th[e] limited scope of discovery is when the plaintiff raises a sufficient question as to the agency’s good faith in processing documents; in such instances, discovery has been permitted.”).

#### **D. FDA Wrongly Demands that ICAN Broaden its Narrow Request**

The FDA cites to *Pinson v. DOJ* to justify its offer to produce the larger universe of non-responsive clinical trials of Engerix-B. In *Pinson*, the agency alleged that the request “lacked specificity and did not align with the manner in which the [agency’s] record system is indexed,”

and the court held that it is the agency's burden to 'provide sufficient explanation as to why such a search would be unreasonably burdensome.'" *Pinson v. DOJ*, 80 F. Supp. 3d 211, 216 (D.D.C. 2015). Similarly, the FDA is claiming here that "[c]linical trial records are not organized in a way that can be readily sorted by such a time period." (Burk Declaration, Dkt. No. 16 at 6). The requirement, therefore, by the *Pinson* court would be "a detailed explanation by the agency regarding the time and expense of a proposed search." *Id.* The FDA has not provided any such detailed explanation. Instead, the FDA submitted five and half pages of a declaration and twenty-nine pages of exhibits regarding a completely irrelevant product.

The FDA also seeks to cast aspersions on ICAN by characterizing it as a frequent requester of clinical trial documents. ICAN's requests are entirely appropriate, especially in light of 21 C.F.R. § 601.51(e) which provides that "[a]fter a license has been issued, the following data and information in the biological product file are **immediately available for public disclosure** unless extraordinary circumstances are shown," including "[a]ll safety and effectiveness data and information" and the "protocol for a test or study." Despite this, it has previously taken the FDA up to almost two **years** to produce just **a subset** of these documents. At best, the FDA is complaining that ICAN is forcing it to comply with its legal obligation.

The FDA also points out previous ICAN requests seeking all clinical trials for other products as a means of demanding it do the same here. ICAN, however, having experienced extremely slow response times and productions in the past, and having to litigate previous requests, wished to simplify the process for this and for future clinical trial requests. It therefore specifically requested a very limited subset of the clinical trials which are, in any event, mandated by law to be made "immediately available to the public." ICAN turned down the FDA's offer to provide

full trials based on its experience as a FOIA requester – including nine previous requests which took an average of more than a year to get documents, one taking as long as 23 months.

Additionally, it is also not appropriate for the FDA to rewrite Plaintiff's FOIA request. ICAN should be free to request a narrower set of clinical trial reports than the entire set of reports for Engerix-B. The FDA did not even offer to limit its production to reports regarding infants and children, a criteria for searching with which it has never taken issue. The FDA would have this Court believe that asking for only certain clinical trials would never be permitted. A clinical trial report is certainly a document subject to FOIA and requesting only certain ones, such as those for a certain vaccine, a certain age group, or a certain period of safety review, is appropriate.

#### **E. The Cases Cited by the FDA are Inapplicable or Inapposite**

The FDA's reliance on *Hall & Assocs. v. EPA* is misplaced. In that case, the requester quoted a statement and asked the responding agency "to provide all documents proving that statement wrong." *Hall & Assocs. v. EPA*, 83 F. Supp. 3d 92, 101 (D.D.C. 2015). That request quite clearly necessitates both research and subjective judgment, unlike ICAN's request, is not asking for the plain reading of documents in an already identified universe.

The request at issue in *Williams v. DOJ*, also cited by Defendant, was one that was "insufficiently specific" where the requester sought "sweeping requests for genealogical and other historical information covering a period of over 600 years with no other identifying details." *Williams v. DOJ*, No. 16 Civ. 512, 2016 U.S. Dist. LEXIS 69613, at \*14-15 (D. Md. May 27, 2016). Here, the instant request is plainly not a "sweeping request[...with no other identifying details." The FDA cannot be permitted to object to requests that are too sweeping and overbroad in some instances and, in other instances, object to those too narrow and specific. This would require a requester to land perfectly in the middle – a middle determined only by the FDA.

Similarly, *Yagman v. Pompeo* is inapposite. That court held that the requester was “not require[d] to identify documents or databases by name, but *some* reasonable description is required.” *Yagman v. Pompeo*, 868 F.3d 1075, 1081 (9th Cir. 2017). Here, ICAN has provided more than “some reasonable description” and the Defendant’s insistence on some unknown precise terminology to make clear the duration for which safety was reviewed is what *Yagman* held was improper. The Defendant knows precisely what is being requested: clinical trials it relied upon to license Engerix-B for babies and children that reviewed safety beyond seven days.

The FDA’s Reply also cites to *Nat’l Sec. Counselors* multiple times for the propositions that “sifting and analysis is not a burden that the FOIA imposes on federal agencies” and that “subjective analysis” should not be required for an agency’s response effort. *See Nat’l Sec. Counselors v. CIA*, 960 F. Supp. 2d 101 (D.D.C. 2013). The request at issue in that case is not analogous to the request here. That request sought “a representative sample of [agency] analytical reports and memoranda presenting psychological analyses or profiles of foreign government officials, terrorist leaders, international criminals, business figures, and other intelligence targets prepared by the [agency]...” and further contained four “guidelines” to define what the requester felt was a “representative sample.” The guidelines demanded a certain number of different types of reports per year, a variety among individuals related to the reports, and a “reasonable variety in the intelligence targets.” This request undoubtedly calls for subjectivity in seeking “representative samples” and “reasonable variety.” ICAN’s request is grounded in a concrete characterization of limited clinical trials already reviewed for safety by the FDA. ICAN seeks *all* clinical trials it relied upon to license Engerix-B for babies and children that fit the criteria of having reviewed safety for 7 days or more. There is no “sifting” or “analyzing” required. The agency does not need to limit the responsive reports to a certain number nor was it asked to provide a variety of

different safety review periods or to determine whether the responsive documents were “representative” samples of any larger category of documents.

## **II. DISCOVERY IS PROPER, RELEVANT AND JUSTIFIED**

“[D]iscovery may be granted when plaintiff has made a sufficient showing that the agency acted in bad faith..., has raised a sufficient question as to the agency’s good faith..., or when a factual dispute exists and the plaintiff has called the affidavits submitted by the government into question.” *Judicial Watch v. United States Dep’t of State*, No. 13-1363, 2016 U.S. Dist. LEXIS 200935, at \*8 (D.D.C. 2016). For the reasons detailed above and in Plaintiff’s letter to the Court, dated September 11, 2020 (Dkt. No. 22), ICAN has raised a sufficient question as to the FDA’s good faith, called into question the FDA’s declarations, and clearly called into question the affidavits submitted by the government.

The FDA has a duty to make “every, reasonable effort” to respond to a FOIA request. 21 C.F.R. § 20.40(b)(2). Because of the FDA’s bad faith claim that it needs “clairvoyant capabilities” to understand the words “safety review period,” Plaintiff asked the FDA for “[a]ll email and electronic documents that contain the phrase ‘safety review period.’” It also sought “[a]ll emails concerning the FOIA request.” Plaintiff’s third discovery request sought “[d]ocuments reflecting the study procedures (a.k.a., clinical protocol or study design) and any summary for each clinical trial involving babies or children that the FDA relied upon to license Engerix-B.” Plaintiff made this limited request to further test the veracity of the FDA’s claimed objections to the instant FOIA request because these study procedures will typically explain the period safety is reviewed in each trial. The one or two page summary for each relevant clinical trial, which likely already exist, would undermine the FDA’s claim that it cannot possibly discern how long safety was reviewed in each clinical trial it relied upon to license this product.

### CONCLUSION

For the foregoing reasons, and for the reasons set out in Plaintiff's cross-motion brief, the Court should grant Plaintiff's cross-motion for summary judgment and order the FDA to disclose all responsive records.

Dated: September 25, 2020

SIRI & GLIMSTAD LLP



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# Exhibit A

Clinical Protocol - Study #442

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Live Attenuated Rubella (RA 27/3) Virus Vaccine

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**Purpose:** To determine antibody and clinical responses to combined live measles-mumps-rubella (RA 27/3) virus vaccine, to combined live measles-rubella (RA 27/3) virus vaccine, and to live attenuated rubella (RA 27/3) virus vaccine.

**Vaccines:** a) Combined live measles-mumps-rubella (RA 27/3) virus vaccine  
Lot No. 621

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

b) Combined live measles-rubella (RA 27/3) virus vaccine  
Lot No. 622

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

c) Live attenuated rubella (RA 27/3) virus vaccine  
Lot No. 579

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial of vaccine should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: The combined vaccines contain egg protein and should not be given to persons with known sensitivity to egg, chicken, or chicken feathers. All three vaccines contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C until used.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccines on ice. Discard unused vaccine 4 hours after rehydration.



Clinical Protocol -

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Study #442

Procedure: The study population will consist of children 1 to 6 years of age.

Children receiving a given vaccine will have a negative history for vaccination with and illness caused by viruses represented in that vaccine. Children will be assigned to receive one of the three vaccines as follows:

<u>Vaccine</u>	<u>Vaccine Lot</u>	<u>No. Children</u>
measles-mumps-rubella	621	150-200
measles-rubella	622	150-200
rubella	579	150-200

Informed consent will be obtained from each child's parent or guardian prior to his participation in the study.

Each child will be bled (10-15 ml) immediately prior to vaccination and 6 weeks following vaccination.

Vaccine dose is 0.5 ml given subcutaneously.

Each child will be followed clinically for 42 days following vaccination. All local and systemic complaints will be recorded on the case report form.

<u>Schedule:</u>	<u>Time</u>	<u>Action</u>
	Day 0	Bleed 10-15 ml. Vaccinate 0.5 ml, subcutaneously.
	Days 0-42	Clinical follow-up for local and systemic reactions.
	Week 6	Bleed 10-15 ml.

Laboratory: Remove sera from clot aseptically and store frozen at -20°C until shipped. It is imperative that sera are sterile to avoid interference with the serologic assay.

Serology: Circulating levels of antibody to each vaccine component will be determined for samples drawn before and after vaccination. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical Forms: Attached.

Clinical Protocol - Study #443

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Live Attenuated Rubella (RA 27/3) Virus Vaccine

**Purpose:** To determine antibody and clinical responses to combined live measles-mumps-rubella (RA 27/3) virus vaccine and to live attenuated rubella (RA 27/3) virus vaccine.

**Vaccines:** a) Combined live measles-mumps-rubella (RA 27/3) virus vaccine, lyophilized  
Lot No. 621

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

b) Live attenuated rubella (RA 27/3) virus vaccine, lyophilized  
Lot No. 579

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single-dose vials. Each vial of vaccine should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water.

**CAUTION:** The combined vaccine may contain egg protein and should not be given to persons with known sensitivity to egg, chicken or chicken feathers. Both vaccines contain neomycin and should not be given to persons with known sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C until used.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

**Procedure:** Establish two groups of 50 to 100 children 1 to 6 years of age as follows:

<u>Group</u>	<u>Vaccine</u>	<u>No. Children</u>
Group 1	measles-mumps-rubella	50-100
Group 2	rubella	50-100

Clinical Protocol -  
Study #443

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Children in Group 1 will have a negative history for vaccination and illness for measles, mumps, and rubella. Children in Group 2 will have a negative history for rubella vaccination and illness.

Informed consent will be obtained from each child's parent or guardian prior to his participation in the study.

Each child will be bled (10-15 ml) immediately prior to vaccination and 6 weeks following vaccination.

Vaccine dose is 0.5 ml given subcutaneously.

Each child will be followed clinically for 42 days following vaccination. All local and systemic complaints will be recorded on the case report form.


Schedule:	<u>Time</u>	<u>Action</u>
	Day 0	Bleed 10-15 ml. Vaccinate 0.5 ml, subcutaneously.
	Days 0-42	Clinical follow-up for local and systemic reactions.
	Week 6	Bleed 10-15 ml.

Serology: Circulating levels of antibody before and after vaccination will be determined. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during this investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused Vaccine: All unused vaccine should be returned immediately to the Virus and Cell Biology Laboratories of the Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.



M. R. Hilleman, Ph.D.



Reference 3

Program: **Study #459** - To evaluate and compare clinical and immunological responses to two combined measles-mumps-rubella virus vaccines and component vaccines of these.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine  
Lot #60664/C-E810  
Combined live measles-mumps-rubella (HPV-77) virus vaccine  
M-M-R  
Live attenuated RA 27/3 rubella virus vaccine  
Lot #60151/C-E665  
Live attenuated HPV-77 + 5 duck embryo cell passages rubella virus vaccine  
MERUVAX  
Live measles virus vaccine  
ATTENUVAX  
Live mumps virus vaccine  
MUMPSVAX  
Rubella placebo

Responsible Clinical Investigator:

Stephen J. Lerman, M.D.  
Assistant Professor of Pediatrics  
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Study Locations:

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James I. Wax, M.D., Omaha, Nebraska  
Joseph R. Ellison, M.D., Omaha, Nebraska  
George D. Maragos, M.D., Omaha, Nebraska  
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Nebraska Medical Center, Omaha, Nebraska  
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William J. McAveney, M.D., Omaha, Nebraska  
Donald T. Glow, M.D., Byron B. Oberst, M.D., Omaha  
Children's Clinic, Omaha, Nebraska  
Yuksel Inankur, M.D., Izzat Jabro, M.D., Dennis Jones, M.D.,  
C. Edwards, M.D., Jim Mulry, M.D., Anthony Romano, M.D.,  
Cogley Clinic, Council Bluffs, Iowa  
Pottawattamie County Immunization Clinic, Lee Martin Therapy  
Center, Council Bluffs, Iowa

Date Study Initiated: May 31, 1977

Date Study Completed: In Progress

Study Procedure:

To date, 257 children have entered the study. Each received a 0.5 ml subcutaneous dose of one of the vaccines. Blood samples were obtained on the day of vaccination and 6 weeks after vaccination, at which time each child received vaccine with those components not in the initial injection. Each child was followed 6 weeks for clinical complaints.

Clinical Protocol - Study #467

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

**Purpose:** To compare antibody and clinical responses to combined live measles-mumps-rubella virus vaccine containing the RA 27/3 rubella virus strain or the HPV-77 duck rubella virus strain.

**Vaccines:** 1. Combined live measles-mumps-rubella (RA 27/3) virus vaccine  
Lot #621

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

2. Combined live measles-mumps-rubella (HPV-77 duck) virus vaccine  
Lot #0131V

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial of vaccine should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water.

**CAUTION:** Both vaccines contain egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. The vaccines also contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. The vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

**Procedure:** The study population will consist of children 1 to 4 years old having a negative history of vaccination for and illness caused by measles, mumps and rubella. Children will be randomly assigned to receive one of the two vaccines as follows:

<u>Group</u>	<u>Vaccine</u>	<u>No. of Children</u>
Group 1	M-M-R (RA 27/3)	100-200 children
Group 2	M-M-R (HPV-77 duck)	100-200 children



Clinical Protocol -  
Study #467

-2-

Informed written consent will be obtained from each child's parent or guardian prior to his participation in the study.

Each child will receive a single 0.5 ml subcutaneous injection of one of the two combined live measles-mumps-rubella virus vaccines.

Bleeding samples (10-15 ml) will be obtained from approximately one-third of the study participants. They will be bled immediately prior to vaccination and 6-8 weeks following vaccination.

Each child will be followed clinically for 42 days following vaccination. All local and systemic complaints will be recorded on the case report form.

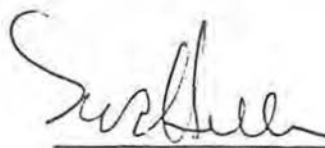
Schedule:	<u>Time</u>	<u>Vaccination and Follow-up</u> (All Children)	<u>Bleeding</u> (Approx. 1/3 of Children)
	Day 0	Vaccinate 0.5 ml, subcutaneously.	Bleed 10-15 ml.
	Days 0-42	Clinical follow-up for local and systemic reactions.	--
	Week 6-8	--	Bleed 10-15 ml.

Serology: Circulating levels of antibody before and after vaccination will be determined. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical  
Forms: Attached.

Adverse  
Reactions: Any serious or alarming reaction, including death due to any cause during this investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused  
Vaccine: All unused vaccine should be returned immediately to the Virus and Cell Biology Laboratories of the Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

  
M. R. Hilleman, Ph.D.

Clinical Protocol - Study #473

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Program: Testing of combined live measles-mumps-rubella vaccines in children.

Purpose: To evaluate and compare clinical and immunological responses to two measles-mumps-rubella virus vaccines.

Vaccines: 1. Combined live measles-mumps-rubella (RA 27/3) virus vaccine  
Lot #621/C-D763

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

2. Combined live measles-mumps-rubella (HPV-77 duck) virus vaccine  
Lot #2127V or 2209V

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial of vaccine should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: Both vaccines may contain egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. The vaccines also contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. The vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccine stored at  $-20^{\circ}$  C.

Keep dried vaccines at  $4^{\circ}$  C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of children 1 to 10 years of age who have a negative history of vaccination for and illness caused by measles, mumps and rubella. The children will be assigned to receive one of the two vaccine as follows:



Clinical Protocol - Study #473  
 Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Procedure: (continued)	Group	Vaccine	No. of Persons
	1	M-M-R (HPV-77 + 5 duck)	up to 200 children
	2	M-M-R (RA 27/3)	up to 200 children

Informed written consent will be obtained from a parent or guardian of each child prior to his participation in the study.

Each child will be bled (10-15 ml) immediately prior to vaccination and 6-8 weeks following vaccination. Each child will receive 0.5 ml of vaccine given subcutaneously.

Each child will be followed clinically for occurrence of local and systemic reactions within 6 weeks following vaccination. Observations should include special notation for rash, nodes, arthralgia, arthritis, fever, malaise, and anorexia. The person(s) observing reactions should not know which preparation the child received.

Schedule:

Time	Action
Day 0	Bleed 10-15 ml. Vaccinate 0.5 ml, subcutaneously.
Days 0-42	Clinical follow-up for local and systemic reactions.
Weeks 6-8	Bleed 10-15 ml.

Laboratory: Remove serum from clot aseptically and store frozen at  $-20^{\circ}$  C.

Serology: Levels of circulating antibody before and after vaccination will be determined. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical  
 Forms: Attached.

Adverse  
 Reactions: Any serious or alarming reaction, including death due to any cause during this investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Arlene McLean, telephone (215) 699-5311, Ext. 6383.

Reference No. 6

Program: Study #484 - To evaluate and compare clinical and immunological responses to two combined live measles-mumps-rubella virus vaccines.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine  
Lot #621/C-D763  
Combined live measles-mumps-rubella (HPV-77) virus vaccine  
M-M-R

Responsible Clinical Investigator:

Anne Gershon, M.D.  
8th Floor North 16  
Bellevue Hospital  
1st Avenue and East 27th Street  
New York, New York 10016

Study Location: New York, New York

Date Study Initiated: December 23, 1976

Date Study Completed: In Progress

Study Procedure:

Sixty-three children, 13 months to 15 years of age, and one adult, have been included in the study thus far. Thirty received a 0.5 ml subcutaneous dose of one of the two vaccines. Thirty-four children received a 1.0 ml subcutaneous dose of combined live measles-mumps-rubella (RA 27/3) virus vaccine. Blood samples were obtained on day of vaccination and 8-12 weeks after vaccination. Each child was followed 6 weeks for clinical complaints. The study continues in progress.

Reference No. 7

Program: Study #511 - To measure antibody and clinical responses to three consecutive lots of combined measles-mumps-rubella virus vaccine.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine, lyophilized

Lot #60664/C-E810

Lot #60665/C-E811

Lot #60666/C-E812

Responsible Clinical Investigator:

Victor M. Villarejos, M.D.  
Director  
Louisiana State University  
International Center for Medical  
Research and Training  
Apartado 10.155  
San Jose, Costa Rica

Study Location: Nicaragua

Date Study Initiated: July 4, 1977

Date Study Completed: September 14, 1977

Study Procedure:

One hundred fifty children, 8 months to 11 years of age, were included in the study. Each received a 0.5 ml subcutaneous dose of combined live measles-mumps-rubella virus vaccine. Blood samples were obtained on day of vaccination and 6 weeks after vaccination. Each child was followed 6 weeks for clinical complaints.



Reference No. 8

Program: Study #513 - To measure antibody and clinical responses to three consecutive lots of combined measles-mumps-rubella virus vaccine.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine, lyophilized

Lot #60664/C-E810

Lot #60665/C-E811

Lot #60666/C-E812

Responsible Clinical Investigator:

Robert E. Weibel, M.D.  
Director, Division of Preventive Medicine  
Joseph Stokes, Jr. Research Institute  
Children's Hospital of Philadelphia  
34th Street and Civic Center Boulevard  
Philadelphia, Pennsylvania 19104

Study Locations:

Lankenau Pediatric Clinic, Philadelphia, Pennsylvania  
G. A. Starkweather, M.D., Havertown, Pennsylvania  
Elizabeth M. Craven, M.D., Wilmington, Delaware  
Pediatric Medical Associates, Havertown, Pennsylvania  
Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Date Study Initiated: June 15, 1977

Date Study Completed: In Progress

Study Procedure:

One hundred sixty-three children, 11 months to 7 years of age, have been included in the study thus far. Each received a 0.5 ml subcutaneous dose of combined live measles-mumps-rubella virus vaccine. Blood samples were obtained on day of vaccination and 6 weeks after vaccination. Each child was followed 6 weeks for clinical complaints. The study continues in progress.

Program: Study #470 - To evaluate and compare clinical and immunological responses to two rubella vaccines, administered alone and in combination with measles virus vaccine.

Vaccine: Combined live measles-rubella (RA 27/3) virus vaccine  
Lot #662/C-D764

Combined live measles-rubella (HPV-77) virus vaccine  
M-R-VAX

Live attenuated RA 27/3 rubella virus vaccine  
Lot #579/C-D418  
Lot #60664/C-E668

Responsible Clinical Investigator:

Louis Z. Cooper, M.D.  
Director, Pediatric Service  
The Roosevelt Hospital  
428 West 59th Street  
New York, New York 10019

Study Location: New York, New York

Date Study Initiated: June 25, 1976

Date Study Completed: In Progress

Study Procedure:

Fifty-four children, 11 months to 18 years of age, have been included in the study thus far. Thirty-six received a 0.5 ml subcutaneous dose of combined live measles-rubella virus vaccine; eighteen received a 0.5 ml subcutaneous dose of live attenuated RA 27/3 rubella virus vaccine. Blood samples were obtained immediately prior to vaccination and six weeks after vaccination from a sample of the population. Each child was followed 6 weeks for clinical complaints. The study continues in progress.

Reference No. 3

Program: Study #512 - To measure antibody and clinical responses to three consecutive lots of combined measles-rubella virus vaccine.

Vaccine: Combined live measles-rubella (RA 27/3) virus vaccine, lyophilized,

Lot #62343/C-F021

Lot #62344/C-F022

Lot #62345/C-F023

Responsible Clinical Investigator:

Victor M. Villarejos, M.D.  
Director  
Louisiana State University  
International Center for Medical  
Research and Training  
Apartado 10.155  
San Jose, Costa Rica

Study Location: Nicaragua

Date Study Initiated: October 11, 1977

Date Study Completed: November 26, 1977

Study Procedure:

One hundred seventy-five children, 10 months to 9 years of age were included in the study. Each received a 0.5 ml dose of combined live measles-rubella virus vaccine. Blood samples were obtained on day of vaccination and 6 weeks after vaccination. Each child was followed 6 weeks for clinical complaints.



**Clinical Protocol - Study #514**

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Program: Combined live measles-rubella virus vaccine

Purpose: To measure antibody and clinical responses to three consecutive lots of vaccine.

Vaccine: Combined live measles-rubella virus vaccine, lyophilized,

Lot no. 62343/C-F021  
Lot no. 62344/C-F022  
Lot no. 62345/C-F023

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water which is supplied in prefilled syringes.

CAUTION: The vaccine should not be given to persons with known sensitivity to neomycin, chicken, eggs or feathers. Persons with leukemia or other immunologic disorder and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccine should not be given to persons with a febrile respiratory illness or other active febrile infection.

Keep dried vaccine stored at -20°C until used.

Keep dried vaccine at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of up to 150 children with a negative history for vaccination and illness caused by measles and rubella viruses. The children should range from 1 to 6 years of age.

Informed written consent will be obtained from a parent or guardian of each child who participates in the study.

Each child will receive a 0.5 ml subcutaneous injection of one of the three vaccine lots.

Bleeding samples (10-15 ml) will be obtained from each child immediately before and 6 weeks after vaccination.

Clinical Protocol - Study #514  
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Procedure:  
(continued)

Each child will be followed clinically for local and systemic complaints occurring within 6 weeks after vaccination. Observations should include special notation for rash, nodes, arthralgia, arthritis, fever, malaise and anorexia. All complaints should be recorded on the case report form.

Schedule:

Time	Action - All Persons
Day 0	Bleed 10-15 ml Vaccinate 0.5 ml, subcutaneously
Days 0-42	Clinical follow-up for local and systemic complaints
Week 6	Bleed 10-15 ml


Serology: Levels of circulating measles and rubella antibodies will be determined by hemagglutination-inhibition test.

Clinical Forms: Attached.

Adverse  
Reactions:

Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Arlene A. McLean, telephone (215) 699-5311, Ext. 6383.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

  
\_\_\_\_\_  
M. R. Hilleman, Ph.D.



# Exhibit B

4-21-89

**MERIEUX INACTIVATED POLIOVIRUS VACCINE**

**FINAL REPORT OF CLINICAL STUDIES AT**

**SUNY/CHILDREN'S HOSPITAL, BUFFALO, NEW YORK  
JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND**

**SUMMARY**

Two doses of Merieux Inactivated Poliovirus Vaccine (M-IPV) at 2 and 4 months of age, followed by a booster dose at 12 months of age, gave excellent neutralizing antibody responses to three types of poliovirus. IPV and OPV alone produced similar levels of neutralizing antibody and IgA in the nasopharyngeal secretions. A combined schedule of IPV and OPV resulted in a slight priming effect after primary immunization for Type II poliovirus by IPV on mucosal immune response of OPV for neutralizing antibody and IgA in the nasopharyngeal secretions and for IgA in the stool. This priming effect was not seen after immunization with a booster dose.

Merieux IPV induced comparable responses in premature and full term infants.

Single and two dose boosters in adults showed high anamnestic responses in all recipients and that a second dose is unnecessary.

There were no significant adverse reactions.

## INTRODUCTION

The Merieux Inactivated Polio Vaccine (M-IPV) produced from continuous cell lines of Vero cells using microcarrier culture has been extensively tested in Finland, Israel, India, Brazil, Indonesia, Mali, France and the United States. This highly purified more potent vaccine has been shown to be safe, highly immunogenic and efficacious when used in a two dose schedule for primary immunization followed by a booster dose.

A clinical trial at Johns Hopkins comparing M-IPV to the oral polio vaccine currently used in the United States, showed that approximately 99% of children had neutralizing antibodies to all three types of polio virus after receiving M-IPV at 2 and 4 months of age, and that a significant boost in titers occurred after the third dose at 18 months of age (Amer. J. Epid. 128: 615-618, 1988). The titers to M-IPV were superior to OPV given in the same 3 dose schedule. This vaccine was made exactly as the Vero cell vaccine intended for license, except the cell substrate for the Johns Hopkins trial was primary monkey kidney cells.

In December 1985, the Office of Biologics requested that 75-100 children and 25-30 adults be immunized according to the United States schedule. In response to this request, clinical studies on children and adults were carried out at

State University of New York/Children's Hospital, Buffalo by Drs. H. Faden and P. Ogra. Supplemental studies on groups of children using three of the four groups tested in Buffalo (only IPV or combined schedules) were initiated at Johns Hopkins by Drs. M. McBean and J. Modlin at a later date.

To meet the FDA request for M-IPV licensure, data are now presented on children and adults from Buffalo and on children only from Baltimore.

#### METHODS

Details of the methods used are outlined in the protocols already submitted under IND. Merieux IPV Lots Z1102, Z1103, A1243, A0301 and A0304 were used. The general approach was to compare immunogenicity of two primary doses of M-IPV, OPV, or a combined schedule in 2 month old children. Originally the recruitment targets were a minimum of 15-20 children each in Groups A, C and D, and 50-60 children were to be recruited in Group B. These numbers were exceeded for all groups. The groups and vaccine schedules are shown below:

#### IMMUNIZATION PLAN FOR CHILDREN

<u>GROUP</u>	<u>2 MONTHS</u>	<u>4 MONTHS</u>	<u>12 MONTHS</u>
A	OPV	OPV	OPV
B	IPV	IPV	IPB
C	IPV	OPV	OPV
D	IPV	IPV	OPV

Buffalo enrolled children in all groups; Johns Hopkins enrolled children in all groups except Group A.

Blood samples for antibody determinations were collected at 2 and 4 months of age just prior to administration of vaccine and one month after the second and third doses of vaccine. A detectable serum neutralizing antibody titer was considered  $>1:10$ ; for neutralizing antibody in the nasopharyngeal secretions and stool  $>1:4$  and for (b) (4) IgA in the NPS and stool  $>1:8$ . GMT's were computed and also expressed in international units based on the FDA reference serum results.

For the adult studies, 30 individuals were immunized and available for the analysis. Half received one dose (Group F1) and half received a second dose 4 weeks later (Group F2). Serum antibody titers were done prior to immunization and 4 weeks after each dose of vaccine.

#### RESULTS IN CHILDREN

M-IPV induced detectable neutralizing antibodies after two doses of vaccine in 97.8% to 100% (Type I), 100% (Type II), and 96.7% to 100% (Type III) of the children (Table 1). Two doses of OPV gave 100% response for all types of poliovirus and a mixed schedule of IPV and OPV induced 96.6% response for Types I and III and 100% response for Type II. The booster dose did not appreciably change the response rates.



The GMT (Table 2) rose approximately 10-fold after two doses and nearly 100-fold post-booster in all groups for Type I. For Type II, two doses of IPV gave lower GMT's than OPV or a mixed schedule, but produced overall even greater titers and fold increases pre- and post-booster than Types I or III. The GMT obtained for Type III with mixed schedules was significantly lower with a mixed regimen of IPV-OPV-OPV than IPV-IPV-OPV or the other two regimens using all IPV or all OPV.

Table 3 presents similar neutralizing antibody data expressed in international units.

Table 4 shows that two primary doses and a booster dose of M-IPV produced neutralizing antibodies in the nasopharyngeal secretions (NPS) in 64% of the children compared to 90% in all OPV recipients and 58% to 68% in recipients of mixed schedules.

After primary immunization, the GMT for Type II was slightly higher in recipients of the IPV-OPV schedule than with OPV alone indicating a priming effect by IPV on OPV-induced antibody (Table 5). The priming effect was not seen post-booster. The NPS neutralizing antibody levels for all types were highest post-booster in children who received only OPV. The data expressed as international units are shown in Table 6.

The percentage of children with IgA antibodies in the NPS (Table 7) were generally at similar levels for M-IPV,

mixed schedule, and OPV for all types of poliovirus after only two doses but were highest in children receiving the mixed schedule of IPV-OPV-OPV. This advantage disappeared post-booster in favor of the all OPV schedule. This pattern was also reflected in the GMT (Table 8).

The percentage of children receiving only IPV with detectable neutralizing antibody in the stool was less than 15% and did not show any appreciable change even after a booster (Table 9). Recipients of either of the mixed schedules or only OPV developed substantial increases in stool antibody, ranging from 23% to 57% for the three types post-booster. Both the percentage with antibody and the GMT were highest for Type II (Tables 10 and 11).

As was the case with neutralizing antibody in the stool, the percentage of children with detectable IgA levels in the stool was essentially unchanged following primary and booster doses of only IPV (Table 12). The mixed schedules resulted in approximately 35% detectable IgA for all three polio types and OPV only ranged from 35% to 55% detectable IgA. The GMT followed a similar pattern (Table 13).

Premature and full-term infants responded equally to primary and booster doses of M-IPV. The percent with detectable antibody titers was essentially 100% to all three types of poliovirus (Tables 14, 15, 16).

### RESULTS IN ADULTS

Nearly all adults had detectable neutralizing antibodies at the time of entry into the study, so that a single dose of M-IPV ensured a 100% response (Table 17).

A single dose of M-IPV induced increases in GMT of nearly 30-fold for Type I, 50-fold for Type II and 125-fold for Type III. A second dose of IPV did not significantly increase the GMT compared to only a single dose.

The results of neutralizing antibodies in the NPS (Table 18) show that the percent of subjects with detectable antibody was the same with one or two doses, suggesting that a greater increase over base titer and higher GMT is obtained in individuals who had a lower antibody titer upon entry.

In contrast, both the percent of individuals with stool neutralizing antibody and the GMT were higher in adults receiving two doses of M-IPV compared to only one dose (Table 19).

The IgA antibody levels in the NPS and stool were similar for one or two doses, although there was a higher percentage of detectable antibody in NPS of recipients of two doses compared to one dose of M-IPV (Tables 20 and 21).

There were no major differences in antibody responses whether there was exposure or nonexposure to OPV (Tables 22 and 23).



ADVERSE REACTIONS

There were no serious adverse reactions reported at either Buffalo or Johns Hopkins.

The Johns Hopkins protocol was set up to include telephone follow up with the patients at 24 hours, 2 and 3 days after each polio immunization to inquire about adverse reactions. Surveillance at Buffalo was limited to an interview during each immunization visit and no adverse experiences were reported other than one adult complaining of redness at the injection site.

Johns Hopkins enrollment is shown below:

<u>Group</u>	<u>No. Enrolled</u>	<u>No. Completing Study</u>
B	54	44
C	16	14
D	16	16

The reactions were summarized as follows:

<u>Immunization #</u>	<u>No. of Reaction Forms</u>	<u>No. Children with &gt;100.6</u>	<u>% with Temps. &gt;100.6</u>
1	86	9	10
2	79	14	18
3	75	5	7

There were no serious local or systemic reactions in any of the children in this study.

✱ Most of the children received DTP at the same time they received the IPV or OPV at 2 and 4 months of age.

One child had a temperature of 103, four children experienced temperatures of 102.

Of the 9 children who had temperatures 100.6 or greater at the time of the first polio immunization, 7 also had local reactions to DTP.

Of the 14 children who had temperatures 100.6 or greater at the time they received the second polio immunization, 9 also had local reactions to DTP. Four of these children received OPv at this time.

Of the 5 children with temperatures 100.6 or greater at the time of the third polio immunization, 2 had colds.

#### DISCUSSION

This study has demonstrated that two primary doses of M-IPV given at 2 and 4 months of age followed by a booster dose at 12 months of age produce excellent neutralizing antibody responses to all three types of poliovirus. The percentage of children with detectable antibody to the Vero cell vaccine was comparable to and the GMT's higher than results obtained in the earlier Johns Hopkins/CDC/FDA study with M-IPV produced in primary monkey kidney cells.

Two children (b) (6), immunized at the same private clinic with two doses of M-IPV, formed good neutralizing antibody titers to Type II but not to the Types I and III poliovirus. The Type II baseline titer and titer one month post 12-month booster, was 320 for both children. The Types

I and III titers at baseline and post-booster were for (b) (6) 10 and <10 and 40 and 20, respectively; for (b) (6) 10 and <10 and <10 and 20, respectively. Both children had normal IgG at 5 months of age and measurable tetanus antibody levels at 13 months of age. It appears the children were immunocompetent, but the reason for poor Types I and III response are unclear.

This study has shown that children given two doses of only OPV or only M-IPV produce similar levels of neutralizing antibodies and IgA in the NPS. Following the booster dose, the number of children with neutralizing antibody and the neutralizing antibody level increases further but is approximately one-half that for OPV in IPV recipients. Nevertheless this level of neutralizing antibody produced by enhanced IPV in the nasopharyngeal secretions is noteworthy.

The strong priming effect of one dose of M-IPV on the mucosal antibody induced by a dose of OPV seen earlier in the primary immunization phase of the study is not maintained in the GMT following booster doses. One month after the booster dose, either of the mixed schedules induced lower GMT's than a schedule of only OPV. Nevertheless, these data clearly show that enhanced M-IPV stimulates local immunity when used alone or in a combination schedule with OPV.

Based on stool antibody data, "gut immunity" appears to be a concept applicable to both M-IPV and OPV. Both vaccines

used alone or in combination gave detectable neutralizing antibody in the stool with similar GMT's.

Because approximately 25% of the infants receiving two doses of IPV were premature births, it was possible to compare responses to full-term infants. Although full-term infants had higher maternal antibody levels, as expected, both premature and full-term infants had similar percentages of responders and comparable GMT's after two doses of IPV.

The studies in adults showed that a single dose of M-IPV produced booster responses with very high titers of neutralizing antibodies and that a second dose is unnecessary. However, stool neutralizing antibody levels were higher in adults receiving a second dose of IPV.

# Exhibit C



**PRODUCT LICENSE APPLICATION**

PLA-0002-XXX-HC48

vol. 2

Merck and Co., Inc.

**Haemophilus b Conjugate Vaccine**

(Meningococcal Protein Conjugate)

8-6-2



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ime Sequence No. 000194

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MERCK SHARP & DOHME RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC.  
WEST POINT, PENNSYLVANIA 19486

KENNETH R. BROWN, M.D.  
GROUP DIRECTOR  
REGULATORY AFFAIRS, BIOLOGICS

(215) 834-2552  
(215) 661-5000

August 31, 1988

Paul D. Parkman, M.D., Director  
Center for Biologics Evaluation and Research  
ATTN: Division of Biological  
Investigational New Drugs - HFB 220  
Parklawn Building - Room 9B-04  
5600 Fishers Lane  
Rockville, Maryland 20857

Serial No. 028

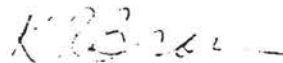
Dear Dr. Parkman:

BB-IND 1966: Haemophilus b Conjugate Vaccine  
(Neisseria meningitidis Outer Membrane Protein Complex)

INFORMATION AMENDMENT - CLINICAL

We are submitting a status report of clinical information that has been generated thus far to support our license application for PEDVAX-HIB™ [Haemophilus b Conjugate Vaccine (Neisseria meningitidis Outer Membrane Protein Complex)]. This information also has been supplied to Dr. Arthur Elliott for submission as an amendment to the license application for this product.

Sincerely yours,



Kenneth R. Brown, M.D.  
Group Director  
Regulatory Affairs, Biologics

CS/ys  
284H

Attachments (3)  
Federal Express No. 9024437752  
9024437763

Desk Copy: Dr. Carl Frasch, HFB-640, Bldg. 29, Room 124  
Federal Express No. 9024437774

Haemophilus B Conjugate Vaccine  
(Neisseria meningitidis Outer Membrane Protein Complex)

## II. SUMMARY

Haemophilus B Conjugate Vaccine (Neisseria meningitidis Outer Membrane Protein Complex), PRP-OMPC has been evaluated in clinical studies of safety and tolerability, anti-PRP titer and subclass responses, and functional activities of vaccine-induced antibodies. The data presented herein were obtained using the vaccine formulation intended for commercial use, i.e., vaccine reconstituted with aluminum hydroxide diluent and administered by intramuscular injection. Results from early studies using other formulations (e.g. vaccine reconstituted with saline diluent) are presented in Section VII (Individual Study Summaries and Tables).

Data on PRP-OMPC were derived using 4 lots of vaccine, including 3 clinical consistency lots; data for polysaccharide vaccines were derived using 3 licensed, nonconjugated polysaccharide (PRP) vaccines (b-CAPSA®, HibVAX™, HIB-IMUNE®). Children 12 to 71 months of age received a single injection of PRP-OMPC. Infants less than 12 months of age were given 2 injections administered 2 months apart. Each dose of PRP-OMPC vaccine contained 15 mcg polysaccharide. Licensed, nonconjugated polysaccharide vaccines were administered in a single injection in 25 mcg doses; children immunized were ≥18 months of age. The number of children vaccinated as of May 16, 1988, the date of data cutoff for this report, and the number with specified data are shown in Table 1. Since studies are continuing, data on safety and immunogenicity are expected from additional vaccinees.

PRP-OMPC vaccine was generally administered alone except in a subset of vaccinees who received other pediatric vaccines (MMR, DTP plus OPV) concurrently but at separate sites with separate needles for injectable vaccines. These studies are in progress and the limited data available for this report are presented.

Vaccinees were evaluated for safety, tolerability and antibody responses. Safety data were obtained for 5 days postvaccination and were based on parents' entries made in a vaccination card provided. Injection site and systemic reactions were reported without regard to causality. Parents' observations recorded on the vaccination cards frequently included entries for intercurrent illnesses whose causal relationship to vaccination was unclear. Evaluation of antibody responses included total antibody determination by a radioimmunoassay (RIA) procedure, quantitation of antibody isotype (IgM, IgG), IgG subclasses, assays for complement-mediated bacteriolysis and opsonization, and passive protection of infant rats.



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III. DESCRIPTION OF PROCEDURES

A. Study Design

Clinical studies of Haemophilus b conjugate vaccine (Neisseria meningitidis outer membrane protein complex) (PRP-OMPC) involved only healthy children aged approximately 2 months to 5 years. To assure an even distribution of children across this age span, vaccinees were grouped into ages 2 to 6 months, 7 to 11 months, 12 to 17 months, 18 to 23 months and 24 to 71 months. The vaccination regimen consisted of two intramuscular injections given 2 months (42 to 70 days) apart in infants below 12 months of age and a single injection in children 12 months of age and older. Each dose of PRP-OMPC vaccine contained approximately 15 mcg PRP. Four clinical vaccine lots were used in the majority of studies: 1069/C-P241, 1072/C-P298, 1080/C-P749, 1085/C-R132, the latter three of which were manufactured for the purpose of demonstrating clinical consistency. In earlier studies conducted on a small scale, vaccine lots 984/C-K731, 1002/C-L466, 1003/C-L680, 1018/C-M679 and 1020/C-N084 were used, in vaccine doses ranging from 6 to 20 mcg polysaccharide.

Institutional Review Board approval and written parental informed consent were obtained prior to enrolling a child in any of the studies. Instruction on vaccine reconstitution, dosage and administration were provided to the investigator by protocol and discussed at site visits. Vaccine was initially stored frozen at -70°C, but later at 2-8°C, as was the diluent.

Blood samples were obtained prior to each injection and approximately 1 month after the second or after a single injection. Only assay results from blood samples obtained within 3 to 7 weeks of the second or only injection of vaccine were analyzed.

All vaccine recipients were observed for at least 15 minutes after vaccination for any immediate reactions. Safety was further evaluated by requiring parents to record their child's temperature and any reactions at the injection site or systemic complaints on the day of vaccination and for 5 days thereafter on Vaccination Report Cards. Serious adverse experiences in the 14 days following vaccination were required to be reported by the investigator. The report included the investigator's opinion on causality of the adverse experience.

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#### IV. INTEGRATED SUMMARY OF SAFETY

Vaccine safety and tolerability were assessed by monitoring postvaccination reactions. Immediately after each injection, children were observed for approximately 15 minutes. Thereafter, reactions were monitored using standardized cards containing specific parameters which were checked by the parents. Reactions for which feedback was required were temperature, injection site reactions (pain/soreness, swelling, redness) irritability, crying, tiredness/sleepiness, hives/rashes, wheezing, nausea, vomiting and diarrhea. Other reactions or conditions not specifically asked for were recorded by the parent in a space provided on the card. The duration of observation varied from 3 to 5 days after the day of vaccination. In addition, any adverse experience occurring within 14 days of vaccination, without regard to causal relationship to vaccination, was recorded. A study site staff member contacted the child's parents during the 24-48 hour period following vaccination. If a parent did not return the vaccination card, information obtained by telephone was used for safety evaluation.

These procedures were expected to insure that serious adverse experiences would not be missed, that reactions previously reported in association with Haemophilus influenzae type b (Hib) polysaccharide vaccines would be sought actively, and that pre-existing conditions were recognized e.g. teething, which would result in symptoms or signs that could be confused with those due to vaccination. This reliance on parental observation, however, resulted in multiple entries including those of a remote or doubtful causal relationship to vaccination.

Four vaccine lots (1069/C-P241, 1072/C-P298, 1080/C-P749, 1085/C-R132), the last three of which represent a clinical series, were used in most of the vaccinees reviewed for safety. Safety data were obtained from children immunized with previous vaccine lots which were also reconstituted and administered in a method similar to that used for the four current lots, i.e., aluminum hydroxide diluent and injection by intramuscular route.

# Exhibit D



### GENERAL SUMMARY

Clinical studies with the yeast recombinant hepatitis B vaccine were initiated in July 1983. This document includes data from studies concerned with the vaccine's safety, immunogenicity and efficacy which were generated to support a license for the vaccine in the United States. Summaries and analyses across studies of clinical complaints and serologic responses are based on data encoded within the project database by October 15, 1985. However, several individual study summaries are derived from more recent data that have not yet been entered in the database.

### VACCINE

A total of 28 lots of yeast recombinant hepatitis B vaccine have been prepared by Merck and Co., Inc., according to procedures developed in the Merck, Sharp and Dohme Research Laboratories. Eighteen of the lots are in use in human clinical trials (see Appendix I). All clinical data received to date indicate that the vaccine is safe. One of the lots (C-J625) was made using (b) (4) procedure and was (b) (4). The clinical and serologic data relating to this lot will be summarized separately, because this procedure will not be used in making commercial vaccine (see section entitled (b) (4) VACCINE). The remainder of the lots were made using a (b) (4) procedure and are in clinical trials under BB IND 1925.

### CLINICAL STUDIES

Table 1 lists 50 clinical studies involving the yeast recombinant hepatitis B vaccine produced by the (b) (4) procedure that are currently in progress.

In most of the studies, participants receive the vaccine as an intramuscular injection administered at 0, 1 and 6 months. However, chronic carriers of HBsAg and certain groups of dialysis patients receive a total of 6 doses of vaccine administered at monthly intervals, while persons with prior immunity and subjects in the study designed to demonstrate noninfectivity of the vaccine are given only a single dose of vaccine. Patients with hemophilia receive the vaccine as a subcutaneous injection. Each dose of vaccine (total mcg of HBsAg administered at a given time) is generally contained within a single injection. However, each 40 mcg dose given to dialysis and predialysis patients consists of a pair of 20 mcg injections.

The numbers of subjects who have received first, second and third injections of the yeast recombinant hepatitis B vaccine are shown by population in Table 2. A total of 3861 participants have received one or more injections of vaccine, while 2309 individuals have completed a 3 dose regimen of vaccination.

Vaccinees in all studies are asked to record their temperature daily and to record any local or systemic complaints that they may have for 5 days following each injection of vaccine. Table 2 also shows by population the number of subjects for whom post vaccination clinical reports are currently available. Clinical reports following the first injection have been received for 2878

PROGRAM: Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 809

PURPOSE: To evaluate antibody and clinical responses to various doses of vaccine in the following initially seronegative populations:

1. Healthy Children (1-11 years of age)
2. Healthy Adults

VACCINE: Yeast Recombinant Hepatitis B Vaccine  
Lot # 972/C-K444 (10 mcg HBsAg/ml)  
985/C-K732 ( 5 mcg HBsAg/ml)

PRINCIPAL INVESTIGATOR: Drs. Stanley Plotkin and Stuart Starr  
Division of Preventive Medicine  
Joseph Stokes, Jr. Research Institute  
Children's Hospital of Philadelphia  
34th Street and Civic Center Blvd.  
Philadelphia, PA 19104

STUDY LOCATIONS: The Pediatric Medical Associates  
420 Township Line Road  
Havertown, PA 19083

George A. Starkweather, M.D.  
1001 Pennsylvania Avenue  
Havertown, PA 19083

DATE INITIATED: February 2, 1984

DATE COMPLETED: In progress

STUDY POPULATION: The study population consists of healthy children (ages 1-11 years) and healthy adults who are negative for HBsAg, anti-HBc, and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

25281/1  
12/31/85



**Study 809****PROCEDURE:**

Children in the study receive a 0.5 ml (5 mcg HBsAg) or a 0.25 ml (2.5 mcg HBsAg) intramuscular injection of lot # 972/C-K444 vaccine at 0, 1 and 6 months or a 0.5 ml (2.5 mcg HBsAg) or 0.25 ml (1.25 mcg HBsAg) injection of lot # 985/C-K732 vaccine according to the same time schedule. Adults receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of lot # 972/C-K444 vaccine at 0, 1 and 6 months. Vaccine recipients (or the parent or guardian in the case of a minor) are asked to record their temperature daily for five days after each injection of vaccine and to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) is obtained from each prospective vaccine recipient one to two weeks before the first vaccination. Post-vaccination bleedings are obtained at 1, 3, 7 and 12 months from some of the children and at 2, 6, 8 and 12 months from others. Post-vaccination bleedings are obtained from adult vaccine recipients at 1, 2, 3, 6, 8, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may also be tested for yeast antibody and those with an anti-HBs titer  $\geq 25$  mIU/ml may be tested for the proportions of anti-a and anti-d activity.

**RESULTS:****HEALTHY CHILDREN:**

1.25 mcg Lot # 985/C-K732 at 0, 1, and 6 months  
 2.5 mcg Lot # 985/C-K732 at 0, 1, and 6 months  
 2.5 mcg Lot # 972/C-K444 at 0, 1, and 6 months  
 5 mcg Lot # 972/C-K444 at 0, 1, and 6 months

**1. Number Vaccinated:**

<u>Dose Level</u>	<u>Injection No.</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
1.25 mcg	26	26	25
2.5 mcg	32	32	30
5 mcg	22	22	21

**Study 809****RESULTS: (Cont.)****2. Serologic Results:**

Serologic data are available for 14, 22, and 14 participants at 7/8 months, who received 1.25 mcg, 2.5 mcg and 5 mcg injections of vaccine, respectively. One hundred percent of the subjects (all dose levels) seroconverted (S/N  $\geq 2.1$ ) and developed protective levels of anti-HBs (mIU/ml  $\geq 10$ ) at that time. Anti-HBs responses and GMTs for 7/8 month data are summarized in the following table.

Dose Level	% with Anti-HBs		GMT (mIU/ml)		
	S/N $\geq 2.1$	mIU/ml $\geq 10$	All Vaccinees	Responders S/N $\geq 2.1$	Responders mIU/ml $\geq 10$
1.25 mcg	100(14/14)	100 (14/14)	2181.1	2181.1	2181.1
2.5 mcg	100(21/21)	100 (21/21)	6230.2	6230.2	6230.2
5 mcg	100(14/14)	100 (14/14)	15965.5	15965.5	15965.5

Among participants with serology data at 12 months, 100% (9/9), 95% (18/19) and 100% (13/13) were positive for anti-HBs (mIU/ml  $\geq 10$ ) from dose level 1.25 mcg, 2.5 mcg and 5.0 mcg, respectively. The GMTs for all vaccinees from these dose levels were 819.2, 3051.5, and 3481.6 mIU/ml, respectively.

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

**3. Clinical Complaints:**

Clinical follow-up data are available for at least 25, 30, and 18 participants, after each injection, in the 1.25 mcg, 2.5 mcg, and 5 mcg dose level, respectively. The overall frequencies of complaints follow.

**Study 809****RESULTS (CONT.):**

<u>Type of Complaint</u>	<u>Dose Level</u>	<u>Frequency in % by Injection No.</u>		
		<u>1</u>	<u>2</u>	<u>3</u>
Injection Site	1.25 mcg	0(0/26)	0(0/26)	4(1/25)
	2.5 mcg	6(2/32)	3(1/31)	0(0/30)
	5.0 mcg	0(0/21)	6(1/18)	0(0/20)
Systemic	1.25 mcg	19(5/26)	12(3/26)	12(3/25)
	2.5 mcg	19(6/32)	13(4/31)	7(2/30)
	5.0 mcg	14(3/21)	22(4/18)	5(1/20)

Refer to Tables 2 through 4 for listings of specific complaints by injection number and dose level. Maximum temperature data are provided in Tables 5 through 7.

There have been no serious or alarming reactions attributable to vaccine.

**PROGRAM:** Yeast Recombinant Hepatitis B Vaccine, Study 865

**PURPOSE:** To evaluate antibody and clinical responses to two or three 5 mcg doses of vaccine among healthy infants and children, ages 3 months through 11 years, who are seronegative for hepatitis B markers.

**VACCINE:** Yeast Recombinant Hepatitis B Vaccine  
Lot # 985/C-K732 (5 mcg/ml)

**PRIMARY INVESTIGATOR:** Prof. E. K. Yeoh, M.D.  
Consultant Physician  
Medical A Unit  
Queen Elizabeth Hospital  
Wylie Road  
Kowloon, Hong Kong

**SECONDARY INVESTIGATOR:** W. K. Chang, M.P., B.S., F.R.C. Path.  
Consultant Microbiologist  
Queen Mary Hospital  
Pokfulam Road  
Hong Kong

Ching Lung Lai, M.B., M.R.C.P., F.R.C.P.  
Consultant Physician  
Queen Mary Hospital  
Pokfulam Road  
Hong Kong

**STUDY LOCATION:** Queen Elizabeth Hospital  
Wylie Road  
Kowloon, Hong Kong

Queen Mary Hospital  
Pokfulam Road  
Hong Kong

**DATE INITIATED:** 2/1/85

**DATE COMPLETED:** In progress

**STUDY POPULATION:** The study population will consist of 100-200 infants and children, ages 3 months through 11 years, who are negative for hepatitis B serologic markers and have not previously received any hepatitis B vaccine.

23921/00851/1  
1/18/86

**Study 865****PROCEDURE:**

Participants are randomly assigned to one of 2 groups with 50-100 children or infants in each group. Group one receives intramuscular injections of vaccine at 0 and 1 month (5 mcg doses). Participants in group 2 receive their injections at 0, 1 and 6 months. The parent or guardian is asked to record the child's temperature for 5 days after each injection and note any local or systemic complaints.

Blood samples are obtained prior to vaccination and at 1, 3, 6, 8, 12 and 24 months post initial injection. All samples are assayed for HBsAg, anti-HBs, anti-HBc and ALT by Dr. Yeoh. Some samples may be tested for yeast antibody at MSDRL. Samples with an anti-HBs titer  $\geq 25$  mIU/ml may be tested to determine anti-a and anti-d activity.

**RESULTS:****HEALTHY INFANTS AND CHILDREN:**

5 mcg Lot #985/C-K732 at 0 and 1 month  
5 mcg Lot #985/C-K732 at 0, 1, and 6 months

**1. Number Vaccinated:**

<u>Group #</u>	<u>Dose Level</u>	<u>Injection No.</u>		
		<u>1</u>	<u>2</u>	<u>3</u>
1	5 mcg	90	70	-
2	5 mcg	88	72	46

**2. Serologic Results:**

Serologic data at 6 months are available for 24 participants in the two injection regimen. At that time 98% (49/50) of the children seroconverted (S/N  $\geq 2.1$ ) for anti-HBs and 94% (47/50) developed protective levels of antibody (mIU/ml  $\geq 10$ ). Among the 21 participants for whom 8 month serologic data are available in the three injection regimen, 100% (21/21) seroconverted and developed protective levels of antibody (mIU/ml  $\geq 10$ ).

A large boost in titer was seen among those children who received the third injection. Geometric mean titers at 8 months were 1894.8



**Study 865****RESULTS (CONT.)**

mIU/ml and 84.50 mIU/ml for those in the three and two injection groups, respectively. Table 1 lists seroconversion rates and GMTs for one to three months of follow-up.

**3. Clinical Complaints:**

Clinical follow-up data are available for 142, 117 and 25 participants following injections one, two and three, respectively.

<u>Type of Complaint</u>	<u>Frequency in % by Injection</u>		
Injection Site	2 (3/141)	2 (2/116)	0 (0/25)
Systemic	6 (8/141)	4 (5/116)	4 (1/25)

There have been no serious or alarming adverse experiences attributable to the vaccine.

00691

PROGRAM: Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine,  
Study 891

PURPOSE: To compare the antibody and clinical responses to recombinant hepatitis B vaccine and plasma-derived hepatitis B vaccine among healthy adults and children who are negative for hepatitis B virus serologic markers.

VACCINES: 1. Yeast Recombinant Hepatitis B Vaccine  
Lot 979/C-K564 (10 mcg HBsAg/ml)  
2. Plasma-Derived Hepatitis B Vaccine  
Lot 0027L (20 mcg HBsAg/ml)

PRIMARY INVESTIGATOR: Dr. Hu Zong-Han  
Department of Biological Products Inspection  
Bureau of Pharmaceutical and Biological Inspection  
Ministry of Health  
Temple of Heaven, West Gate  
Beijing, People's Republic of China

SECONDARY INVESTIGATOR: Dr. Shi Guiyong  
Director of Epidemic Department  
Chinese Medical University  
Shen Yang, People's Republic of China

STUDY LOCATION: Shen Yang Municipal Anti-Epidemic Station  
Shen Yang, People's Republic of China

DATE STUDY INITIATED: December, 1985

DATE STUDY COMPLETED: In progress

STUDY POPULATION: The study population consists of 200 healthy adults and 200 healthy children of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

32121/1  
1/17/86

00692

**Study 891****STUDY PROCEDURE:**

Participants are grouped by age and randomly assigned to receive the yeast recombinant or plasma-derived hepatitis B vaccine as follows:

Group	Population	Vaccine	Dose	Number	Regimen
1	Adults (≥30 years)	Recombinant	10 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
2	Adults (18-29 years)		10 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
3	Children (5-10 years)		5 mcg	100	0.5 ml intramuscular injection of vaccine at 0, 1, and 6 months
4	Adults (≥30 years)	Plasma	20 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
5	Adults (18-29 years)		20 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
6	Children (5-10 years)		10 mcg	100	0.5 ml intramuscular injection of vaccine at 0, 1, and 6 months

Study participants or the participant's parent or guardian record their temperature or that of their child, and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two to three weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 7, 8, 9, 12, and 24 months. All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT.

32121/2  
1/17/86

00693

**Study 891**

**RESULTS: (Contd)**

To date 100 adults and children have received one injection of yeast recombinant or plasma-derived hepatitis B vaccine. No serious or alarming reactions attributable to vaccination have been reported. Clinical follow-up data and serologic results are not yet available. The study continues in progress.

32121/3  
1/17/86

# Exhibit E



Reference No. 85-053

Drug Licensed Name: Hepatitis B Vaccine  
(Recombinant)

Mfr: Merck Sharp &amp; Dohme (MSD)

Drug Trade Name: RECOMBIVAX HB®

Hepatitis B Vaccine (Recombinant), RECOMBIVAX HB, is a non-infectious subunit viral vaccine derived from synthetic hepatitis B surface antigen (HBsAg) produced in yeast cells. A plasmid containing a portion of 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.

## I. INDICATIONS FOR USE:

RECOMBIVAX HB is indicated for immunization against infection caused by all known subtypes of hepatitis B virus (HBV). The vaccine has been shown to be effective in inducing an immune response (anti-HBs) in initially seronegative adults and children. It has been shown to be effective in preventing chronic hepatitis B infection among infants of carrier mothers when used in conjunction with one dose of hepatitis B immune globulin.

RECOMBIVAX HB will not prevent hepatitis caused by other agents such as hepatitis A virus, non-A, non-B hepatitis viruses or other viruses known to infect the liver.

Vaccination is recommended for those persons who are or will be at increased risk of infection with all known subtypes of hepatitis B virus, including persons employed in a variety of health care occupations, patients requiring frequent and/or large volume blood transfusions or clotting factor concentrates, residents and staff of institutions for the mentally handicapped, intimate contacts of persons with persistent hepatitis B antigenemia, infants born to HBsAg positive mothers, persons at increased risk due to their sexual practices, and users of illicit injectable drugs. Additional studies are in progress in dialysis patients.

Studies are ongoing to determine the need and timing for revaccination.

## II. DOSAGE AND ADMINISTRATION:

RECOMBIVAX HB consists of hepatitis B surface antigen which is produced in yeast cells. The isolated and purified antigen is adsorbed onto aluminum hydroxide as an adjuvant, and thimerosal is added as a preservative. A 1.0 ml dose of the adult formulation of the vaccine

contains 10 mcg of hepatitis B surface antigen adsorbed onto 0.5 mg of aluminum hydroxide; a 0.5 ml dose of the pediatric formulation contains 5 mcg of hepatitis B surface antigen adsorbed onto 0.25 mg of aluminum hydroxide. All formulations of vaccine contain 1:20,000 thimerosal as preservative. The vaccine has been treated with formaldehyde prior to adsorption onto alum.

Primary vaccination consists of three injections of vaccine, with the second and third injections given 1 and 6 months, respectively, after the first. Adults and children above 10 years of age are given 10 mcg (1.0 ml) of hepatitis B surface antigen per injection, while children from birth to 10 years of age receive 5 mcg (0.5 ml) of hepatitis B surface antigen per injection. Infants born to HBsAg positive mothers should receive at birth Hepatitis B Immune Globulin in conjunction with the first dose of RECOMBIVAX HB in different sites. All injections are given intramuscularly in the deltoid muscle in adults and children or in the anterolateral thigh muscle in infants and neonates, except those given to persons with hemophilia or similar disorders which are given subcutaneously. Data suggest that injections given in the buttocks are less effective in producing an immune response, perhaps since injections in the buttocks may frequently be given into fatty tissue instead of into muscle.

### III. MANUFACTURING AND CONTROLS:

#### A. MANUFACTURING AND CONTROLS

The organism, Saccharomyces cerevisiae, strain (b)(4), which is utilized for the production of HBsAg, contains a plasmid containing a gene for the adw subtype of HBsAg. The culture is grown in a Yeast Extract/Soy Peptone/Dextrose (YEH) medium at (b)(4). The fermentations are

(b)(4)

(b)(4)

(b)(4)

(b)(4)

The final container is tested for sterility, general safety, (b)(4) thimerosal, (b)(4) aluminum (b)(4) and potency in mice (b)(4) (b)(4)

The manufacturer submitted for evaluation samples and protocols of five final container lots of vaccine derived from five different bulk lots produced initially at production scale. These lots met the release specifications listed at the time of their manufacture. Subsequently, modifications to the release specifications have been incorporated into the license application. These include a (b)(4) yeast impurity specification from (b)(4) to (b)(4) and a change in the (b)(4) specification for the mouse potency test from 3.0 mcg/ml to 1.5 mcg/ml. The specification requires that (b)(4)

(b)(4) Additional lots have been submitted for release which when tested by the manufacturer meet all of the current release specifications.

#### B. STABILITY STUDIES

The recommended storage temperature of the vaccine, adsorbed onto alum is 2-8°C. Stability of the vaccine was monitored by the demonstration of potency in an in vivo mouse model and by (b)(4) (b)(4) of the vaccine was studied through (b)(4) (b)(4) at 2-8°C. and (b)(4) to 24 months at 2-8°C. No significant differences in potency which would indicate a loss in the immunizing potential of the product were observed throughout the period. Other studies are in process. Accelerated stability studies at (b)(4) were carried out. By the mouse potency assay, statistically significant degradation was noted only at (b)(4) By (b)(4) measurable loss of antigen occurred at temperatures (b)(4) (b)(4)

The product will have an expiration dating of twenty-four months at 2-8°C. The package insert recommends storage at 2-8°C. which is supported by the stability studies. Merck has committed to conduct ongoing stability studies.

C. VALIDATION

The major equipment used in the manufacture and filling of the vaccine has been validated at the Merck & Co., Inc., West Point, PA, facilities. In addition, appropriate specifications have been established for monitoring environmental conditions for critical work areas in this facility by the Environmental Control Department, MSD. Validation analyses for product potency and purity are performed at MSD. The test methods were found to be suitable for control and regulatory purposes.

D. LABELING

The labeling, including the package insert, has been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57 and found satisfactory. The container label includes a warning statement indicating "Do Not Inject Intravenously", a caution statement that federal law prohibits dispensing without prescription, a statement to "Shake Well Before Using", a statement to store at 2-8°C. (35.6 - 46.4°F) and a warning statement "Do Not Freeze." A statement to see the accompanying circular for dosage instructions is also included.

The package insert (copy attached) contains appropriate statements concerning product description, clinical pharmacology, indications and use, contraindications, warnings, precautions, adverse reactions, how supplied, dosage and administration and information on the storage of the vaccine.

E. ESTABLISHMENT INSPECTION

A pre-license inspection of the MSD biological production facilities in West Point, PA, was conducted May 12-14, 1986. No objectionable practices or exceptions to the regulations were observed.


F. ENVIRONMENTAL IMPACT ANALYSIS REPORT

An environmental assessment for the manufacture and use of RECOMBIVAX HB was completed to address the environmental impact considerations of 21 CFR, Part 25. The information provided for this environmental assessment supports the finding of no significant environmental impact. (Exhibit 2)



#### IV. PHARMACOLOGY, BIOCHEMISTRY AND SEROLOGY:

RECOMBIVAX HB is composed of HBsAg which is the product of a plasmid containing a portion of the hepatitis B virus gene that codes for HBsAg and which was derived from plasma of a donor infected with hepatitis B virus, subtype adw. This plasmid has been cloned into yeast. (b)(4)



(b)(4)

Serological studies have been performed to evaluate the anti-HBs antibodies raised in recipients of yeast-derived vaccine. Cross-adsorption studies were performed on anti-HBs in five recipients of yeast-derived vaccine four months post-vaccination and in six recipients of plasma-derived vaccine three months post-vaccination. In all five samples from yeast vaccine recipients 99-100% of the anti-HBs antibodies were adsorbed by both yeast-derived and plasma-derived antigen. In the six samples from plasma-derived vaccine recipients, 99-100% of the anti-HBs antibodies were adsorbed by plasma-derived HBsAg and 87-99% by yeast-derived antigen. The mean affinity constants obtained against a synthetic cyclic peptide derived from the HBsAg sequence were  $4 \times 10^7$  for antibodies from both plasma-derived vaccine recipients and yeast-derived vaccine recipients.

An inhibition assay using a monoclonal antibody that had been shown to protect chimpanzees from hepatitis B infection showed 38% inhibition (10-69%) of the monoclonal antibody by samples from 10 yeast-derived vaccinees and 54% inhibition (18-99%) by samples from 10 plasma-derived vaccinees.

Avidity constants against entire HBsAg ranged from 4 to  $8 \times 10^{10}$  in six samples at 3 months post-vaccination from plasma-derived vaccinees and 1 to  $16 \times 10^{10}$  in six samples from yeast-derived vaccinees.

Comparison of the proportions of the anti-a and anti-d components of the anti-HBs response showed that at 7 months post-vaccination 95% of the anti-HBs was anti-a and 5% anti-d in 27 samples of yeast vaccine recipients and 93% anti-a and 7% anti-d in 8 samples from plasma-derived vaccine recipients.



These serological studies show that although the antibodies induced by yeast-derived and plasma-derived antigen are comparable, 1) yeast-derived antigen is slightly less capable of adsorbing antibody induced by plasma-derived antigen, 2) the antibody induced by yeast-derived antigen is somewhat less reactive in a cross inhibition assay with a protective monoclonal antibody and 3) the antibodies induced by yeast-derived antigen show greater variability in their avidity constants.

V. MEDICAL:

A. GENERAL INFORMATION

Hepatitis B virus is one of several viruses (hepatitis A, hepatitis B and several non-A, non-B hepatitis) causing a systemic infection with pathologic changes in the liver. It is a major cause of acute and chronic hepatitis and cirrhosis and has been implicated in the etiology of primary hepatocellular carcinoma worldwide. There is no effective treatment for hepatitis B infection. Six to 10% of young adults infected with hepatitis B in the United States fail to eliminate the virus and become persistently infected (chronic HBsAg carriers). It is estimated that there are 0.7 to 1.0 million chronic carriers of hepatitis B virus in the United States and more than 170 million in the world.

In the United States and Northern Europe, hepatitis B virus infects mainly adults, while children are most affected in developing areas of the world. In both cases, the virus is maintained in populations primarily by transfer of infection from chronic carriers. Such spread is effected through blood transfusion, exposure to contaminated needles or instruments, through sexual contact and by spread from carrier mother to infant in the perinatal period.

Hepatitis B surface antigen is the main component of the outer envelope of the 42 nm hepatitis B virus. Excess HBsAg is also produced in particles that are 18-22 nm in diameter. HBsAg has been found in the blood and other clinical specimens including saliva, urine, bile and feces of infected persons.

Antibodies to HBsAg (anti-HBs) have been shown to be protective against infection with HBV. A safe and effective hepatitis B vaccine comprised of hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of the virus is commercially available. An attractive alternative to human plasma as a source of HBsAg is the use of recombinant DNA technology to effect synthesis of HBsAg by a culture of microorganisms. Vaccine prepared from yeast by recombinant DNA technology was shown to be safe and antigenic in monkeys and chimpanzees and also protective in chimpanzees subsequently challenged with infectious hepatitis B virus.

**B. CLINICAL STUDIES**

From July 1983 to January 1986 RECOMBIVAX HB was administered to approximately 3800 participants enrolled in 50 clinical studies to assess immunogenicity and safety. The populations included in the studies are summarized in Table 1. In addition, the four studies in infants born to carrier mothers were designed to assess protection from chronic infection.

The vaccine was administered as a series of three intramuscular injections. The first two injections were given one month apart followed by a third or booster injection given six months after the first dose.

Vaccine recipients were asked to report their temperature and any injection site or systemic sequelae that occurred within a five day period following each injection of vaccine.

Post-vaccination blood samples were obtained for the determination of antibody to hepatitis B surface antigen (anti-HBs), other hepatitis B virus serologic markers (HBsAg, anti-HBc), serum alanine aminotransferase (ALT) activity, and in some instances, antibody to yeast antigens.

**1. SAFETY**

The vaccine was proven non-infectious for man in a human safety test in which a single 1.0 ml dose of vaccine containing 10 mcg of HBsAg was administered to each of five initially seronegative persons who were followed serologically for 6 months for appearance of markers of hepatitis B infection. No markers were detected.

RECOMBIVAX HB has been well tolerated. There have been no serious or alarming reactions directly attributable to vaccine reported among subjects who participated in the clinical studies. The types and incidence of complaints which were reported within five days following administration of 3258 injections of vaccine to 1252 healthy adults who participated in clinical studies for which analysis has been completed are summarized in Table 2. Injection site and systemic complaints were reported following 17% and 15% of the injections, respectively. Comparable rates of systemic reactions were observed in controlled clinical studies using plasma-derived vaccine in both the immunized and placebo groups. The most frequent specific injection site reactions were soreness, pain and tenderness. The most frequent systemic complaints were fatigue/weakness and headache.

In the clinical trials, no cases of anaphylaxis, severe bronchospasm or laryngeal edema were reported. There were 3 reports of urticaria, one of facial edema and 16 reports of "rash". Antibodies to yeast have been observed both pre- and post-immunization. Testing for serum IgG and IgE antibodies to yeast proteins in individuals with allergic reactions indicated no correlation between antibody responses to yeast antigens and allergic reactions.

The frequency of clinical complaints reported within five days following administration of 231 injections of vaccine to 80 healthy children (3 months to 11 years) for which analysis has been completed are summarized in Table 3. Systemic complaints including fatigue, weakness, diarrhea and irritability were reported following 14% of the injections. Injection site complaints consisting principally of soreness were reported following 2% of the injection.

## 2. IMMUNOGENICITY

Clinical studies have demonstrated that Hepatitis B Vaccine (Recombinant) induces protective levels of antibody in greater than 90% of healthy individuals who received the recommended three-injection regimen. A protective antibody level has been defined as 10 or more milli-International Units/ml (mIU/ml) as determined by (b)(4).

Anti-HBs responses of 511 healthy adults 20-69 years of age, 83 healthy children, and 53 dialysis patients are summarized in Table 4. The doses used were 3 x 10 mcg for adults, 3 x 5 mcg for children and 3 x 40 mcg for dialysis patients.

Antibody response to the vaccine is age dependent. The younger the vaccinee, the greater the likelihood of an immune response developing. Antibody seroconversion rates for children 1 to 10 years of age were 100% with Geometric Mean Titer (GMT) of 15,966 mIU/ml. Seroconversion rates for adults ranged from 95% to 99% for those 20 to 39 years of age and 91% for those 40 years of age or older. The Geometric Mean Titers (GMT) were 1707 mIU/ml for the 20-29 year age group and 484 mIU/ml for the 40-49 year age group. Immunocompromised persons respond less well to the vaccine than do healthy individuals. Sixty-eight percent of predialysis and dialysis patients who received three 40 mcg doses of vaccine developed protective level of anti-HBs and had a GMT of 178 mIU/ml.

Preliminary data from a double-blind, randomised, controlled study in healthy adults comparing this product and the currently licensed plasma-derived vaccine show at nine months comparable seroconversion rates of 91% (40/44) for the



recombinant vaccine and 93% (38/41) for the plasma-derived one. The GMT (402 mIU/ml) seen in these recipients of the recombinant vaccine was less than half that seen in the recipients of the plasma-derived vaccine (1676 mIU/ml).

### 3. EFFICACY

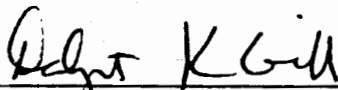
The protective efficacy of RECOMBIVAX HB has been demonstrated in neonates born to mothers positive for both HBsAg and HBeAg. In two clinical studies of infants who received the recommended one injection of hepatitis B immune globulin at birth followed by a three injection regimen of vaccine, efficacy in prevention of chronic hepatitis B infection was 93% in 40 infants at 6 months in one study and 93% in 57 infants at nine months in the other study.

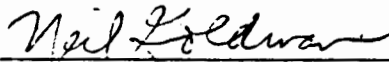
### VI. ADVISORY PANEL CONSIDERATION.


Data concerning the manufacture, safety and efficacy of Hepatitis B Vaccine (Recombinant) for the prevention of hepatitis B were discussed at the Vaccines and Related Biological Products Advisory Committee meeting on June 7, 1984, October 4, 1984 and April 3, 1986.

### VII. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached. (Exhibit 1)

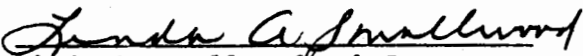
  
Daljit K. Gill, M.D.  
Chairman

  
Neil Goldman, Ph.D.

  
Elizabeth B. Paul

  
Ira Berkower, M.D.

  
Barbara C. Meyer

  
Linda A. Smallwood, Ph.D.