U.S. FOOD & DRUG ADMINISTRATION

September 5, 2023

Aaron Siri
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Sent via email to: aaron@sirillp.com

RE: Citizen Petition (Docket No. FDA-2020-P-2136)

Dear Mr. Siri,

This letter responds to the citizen petition dated October 28, 2020 (the Petition) that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of the Informed Consent Action Network (ICAN) (Petitioner) regarding package inserts and labeling of acellular pertussis vaccines.

This letter responds to the Petition in full. We have reviewed the Petition and other information available to the Agency. Based on our review of these materials, and for the reasons described below, we conclude that the Petition does not contain facts demonstrating any reasonable grounds for the requested action. In accordance with Title 21 CFR (Code of Federal Regulations) 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition.

Here is an outline of our response:



## I. PETITIONER'S REQUEST

The Petition requests that "all manufacturers of acellular pertussis-containing vaccines be required to amend the package inserts of these products to disclose that they do not prevent infection and transmission of pertussis."[1]

## II. BACKGROUND

### A. Licensed Vaccines Are Safe, Pure, and Potent

FDA has a stringent regulatory process for licensing vaccines.[2, 3] The Public Health Service Act (PHS Act) authorizes FDA to license biological products, including vaccines, if they have been demonstrated to be "safe, pure, and potent."[4] Prior to approval by FDA, vaccines are extensively tested in non-clinical studies and in humans. FDA's regulations describe some of the extensive data and information that each sponsor of a biologics license application (BLA) for a vaccine must submit to FDA in order to demonstrate the product's safety before FDA will consider licensing the vaccine. FDA requires that the sponsor's application include, among other things, data derived from nonclinical and clinical studies showing the product's safety, purity, and potency; a full description of manufacturing methods for the product; data establishing the product's stability through the dating period; and representative sample(s) of the product and summaries of results of tests performed on the lot(s) represented by the sample.[5]

As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its proposed indication(s) and use. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to assess whether the safety, purity, and potency of a vaccine has been demonstrated.[6] Only when FDA's standards are met is a vaccine licensed.

FDA regulations explicitly state that "[a]pproval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."[7] Potency has long been interpreted to include effectiveness.[8] FDA has also generally considered "substantial evidence"[9] of effectiveness to be necessary to support licensure of a biological

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[1] Petition at 1.
[2] FDA, Vaccine Development - 101, last updated December 2020, https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101.
[3] FDA, Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[4] Section 351(a)(2)(C)(i)(I) of the PHS Act.
[5] 21 CFR 601.2(a).
[6] FDA, Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[7] 21 CFR 601.2(d).
[8] 21 CFR 600.3(s).
[9] The Federal Food, Drug, and Cosmetic Act, see section 505(d) (21 U.S.C. § 355(d)), defines "substantial evidence" as:

product under section 351 of the PHS Act. Therefore, the manufacturers of vaccines that have been licensed in the United States (U.S.) have necessarily demonstrated the safety and effectiveness of the vaccines within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

FDA's oversight of the safety of vaccines continues after licensure. Once a licensed vaccine is on the market, post-marketing surveillance of vaccine safety is conducted in order to detect any rare, serious, or unexpected adverse events that were not detected prelicensure and to evaluate and verify safety signals, including those that may have been detected prelicensure. FDA employs multiple surveillance systems and databases to continue to evaluate the safety of vaccines. In certain cases, the FDA may require the manufacturer to conduct post-marketing studies to further assess known or potential serious risks.

### B. Standards for Labeling

The labeling requirements for approved prescription drugs and biological products are found in several sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the PHS Act, including: sections 201, 502, and 503 of the FD&C Act and section 351 of the PHS Act. In addition to the aforementioned statutory requirements, FDA regulations document the content and format of prescription drug labeling for approved drugs and biological products.[10] One of FDA's objectives in establishing labeling regulations has been to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[11]

A prescription drug product's FDA-approved Prescribing Information (also known as "professional labeling," "package insert," "direction circular," or "package circular") is a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or BLA submitted by the applicant.[12] It is written for the health care practitioner audience, because prescription drugs require ''professional supervision of a practitioner licensed by law to administer such drug."[13] Labeling is subject to all applicable provisions enumerated under section 502 of the FD&C Act.[14]

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evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

[10] See, e.g., 21 CFR 201.56 and 21 CFR 201.57; see also 21 CFR 201.100(c).

[11] Preamble to final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922 at 3928, January 24, 2006), https://www.federalregister.gov/documents/2006/01/24/06-545/requirements-on-content-and-format-of-labeling-for-human-prescription-drug-and-biological-products (Physician Labeling Rule). For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in § 201.57 (21 CFR 201.57), see § 201.80 (21 CFR 201.80). The specific labeling requirements for older drug products differ in certain respects, and generally are not referenced in this response.

[12] Id. at 3922.

[13] Id. (quoting section 503(b) of the FD&C Act).

[14] Id.

FDA regulations provide that any labeling "that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug" must contain "[a]dequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended[.]"[15] Required information and the specific format for labeling are set out in FDA regulations at 21 CFR §§ 201.56 and 201.57.[16] Labeling is required to be "informative and accurate and neither promotional in tone nor false or misleading in any particular... the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading."[17] As provided for in FDA regulations, "labeling must be based whenever possible on data derived from human experience."[18]

Specific requirements regarding the content and format of labeling are further enumerated under 21 CFR § 201.57, which provides that labeling must include information regarding the approved indication and usage.[19] Additionally, under 21 CFR § 201.57(c)(2), the Indications and Usage section of the full prescribing information must "state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition."

In addition to identifying the disease, condition, or symptom for which a prescription drug or biological product is approved, the Indications and Usage section may also include additional important aspects of indication such as selected patient subgroups or disease subpopulations for whom the product is approved.[20] The Indications and Usage section should not only clearly communicate the scope of the approved indication, but also specify the population to which the determination of safety and effectiveness is applicable.[21]

For biological products, indications "must be supported by substantial evidence of effectiveness."[22] The Clinical Studies section of a vaccine's labeling discusses those clinical studies that facilitate an understanding of how to use the vaccine safely and effectively, this section will describe the studies that support effectiveness for the vaccine's labeled indication(s).[23] Discussion of studies in the Clinical Studies section must not imply or suggest indications not stated in the Indications and Usage section.[24]

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[15] 21 CFR 201.100(d).
[16] Requirements for the labeling of products not subject to the requirements of §201.57 (21 CFR 201.57) are located in §201.80 (21 CFR 201.80).
[17] 21 CFR 201.56(a)(2).
[18] 21 CFR 201.56(a)(3).
[19] 21 CFR 201.57(c)(2).
[20] 21 CFR 201.57(c)(2)(i)(B).
[21] See Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format; Draft Guidance for Industry, July 2018, https://www.fda.gov/media/114443/download.
[22] 21 CFR 201.57(c)(2)(v).
[23] 21 CFR 201.57(c)(15).
[24] 21 CFR 201.57(c)(15)(i).

Labeling must also describe certain information regarding warnings and precautions such as: clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.[25] Additionally, labeling must also include contraindications (situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit).[26]

In addition, FDA regulations in 21 CFR § 201.57(c)(2)(ii) provide that "[i]f there is a common belief that [a] drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section [the Indications and Usage section of the product's prescribing information] state that there is a lack of evidence that the drug is effective or safe for that use or condition."

FDA reviews labeling of prescription drug and biological products prior to approval of a NDA or BLA and continues to assess the adequacy of labeling after approval.

### i. Pre-Approval Review of Vaccine Labeling

Pursuant to 21 CFR § 601.2(a), manufacturers must submit proposed vaccine labeling to FDA as part of a BLA. When reviewing labeling, FDA determines whether the information presented is scientifically accurate, conforms to regulatory requirements set out in 21 CFR §§ 201.56 and 201.57, and includes requested revisions.[27]

In the September 2004 Guidance for Industry entitled "FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information" (September 2004 Vaccine Labeling Guidance), FDA noted that "[a]n important part of vaccine labeling is the package insert. FDA reviews the entire package insert to determine whether it is adequate."[28] FDA further explained in this Guidance, that if the agency "conclude[s] that a proposed vaccine package insert does not contain adequate warnings, use instructions, and precautionary information, [FDA] communicate[s] such findings to the manufacturer as soon as is practicable."[29] When FDA concludes that a vaccine label's warnings, use instructions, and precautionary information have been sufficiently revised to include current information regarding the nature and extent of the dangers posed by such vaccines, FDA formally approves the final draft labeling as described in FDA regulations, see 21 CFR §§ 601.2 and 601.12(f).[30]

### ii. Post-Approval Vaccine Labeling

FDA continues to assess the adequacy of vaccine labeling post-approval. As explained in the September 2004 Vaccine Labeling Guidance, "FDA takes into account various sources of

[25] 21 CFR 201.57(c)(6)(i).
[26] 21 CFR 201.57(c)(5).
[27] FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information; Guidance for Industry, Sept. 2004, at 2, https://www.fda.gov/media/73544/download.
[28] Id.
[29] Id.
[30] Id. at 2-3.

information during our surveillance and review of vaccine labeling requirements for warnings, use instructions, and precautionary information,"[31] including the following:

- The existing labeling requirements listed under 21 CFR §§ 201.56 and 201.57;
- Epidemiological information contained in Morbidity and Mortality Weekly Reports (MMWR), published by the Centers for Disease Control and Prevention (CDC);[32]
- Reports in the medical literature; and
- Summaries from the Vaccine Adverse Event Reporting System (VAERS).[33]

When new information on a vaccine's safety and effectiveness becomes available after licensure, FDA reviews the data to determine whether the Prescribing Information and other labeling should be revised to include this new information.[34] If a vaccine's Prescribing Information does not reflect currently available information regarding the warnings, use instructions and precautionary information, FDA notifies the manufacturer and typically recommends, in such a case, that appropriate revision is necessary.[35]

### C. Pertussis is a Serious Disease

Pertussis, also known as whooping cough, is a serious and highly contagious respiratory disease caused by the bacterium *Bordetella pertussis* (*B. pertussis*).[36] Pertussis can cause uncontrollable and violent coughing that can make it difficult to breathe, and often results in an individual taking deep gasping breaths that produce a "whoop" sound.[37] Pertussis can affect individuals of all ages but is especially serious and even deadly for young children and infants.[38]

In the early 20th century, pertussis was one of the most common childhood diseases and a major cause of childhood mortality in the United States.[39] According to CDC statistics, "[f]ollowing the introduction of pertussis vaccines in the 1940s when case counts frequently exceeded 100,000 cases per year, reports declined dramatically to fewer than 10,000 by 1965."[40]

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[31] Id. at 3.
[32] See CDC, Morbidity and Mortality Weekly Report (MMWR), last reviewed July 2023, http://www.cdc.gov/mmwr/.
[33] September 2004 Vaccine Labeling Guidance, at 3.
[34] Id.
[35] Id.
[36] CDC, Pertussis (Whooping Cough): Causes and How It Spreads, last reviewed August 2022, https://www.cdc.gov/pertussis/about/causes-transmission.html; CDC, Pertussis (Whooping Cough): Signs and Symptoms, last reviewed August 2022, https://www.cdc.gov/pertussis/about/signs-symptoms.html.
[37] CDC, Pertussis (Whooping Cough): Signs and Symptoms, last reviewed August 2022, https://www.cdc.gov/pertussis/about/signs-symptoms.html.
[38] CDC, Pertussis (Whooping Cough): Complications, last reviewed August 2022, https://www.cdc.gov/pertussis/about/complications.html.
[39] CDC, Chapter 16: Pertussis, *in* Epidemiology and Prevention of Vaccine-Preventable Diseases- The Pink Book: Course Textbook - 14th Edition, at 239 (14th ed., 2021), https://www.cdc.gov/vaccines/pubs/pinkbook/pert.html ("Chp. 16: Pertussis, The Pink Book").
[40] CDC, Pertussis (Whooping Cough): Surveillance and Reporting, last reviewed August 2022, https://www.cdc.gov/pertussis/surv-reporting.html.

Whole-cell pertussis vaccines were first licensed in the United States in 1914.[41] Local reactions such as redness, swelling, and pain at the injection site occurred following up to 50% of doses of whole-cell pertussis vaccines, fever and other mild systemic events were also common.[42] Concerns about these reactions led to the development of more purified (acellular) pertussis vaccines, which are associated with a lower frequency of adverse reactions.[43] Vaccines licensed for use in the United States to prevent pertussis include an "acellular pertussis" component which, depending on the particular vaccine, is comprised of three or more purified antigens of *B. pertussis*.[44] All currently licensed U.S. vaccines for prevention of pertussis contain an acellular pertussis component, there are no longer any whole-cell pertussis vaccines licensed in the United States.[45]

With regard to pertussis, the CDC states that "[t]he best way to prevent whooping cough is to get vaccinated."[46] Currently FDA licensed vaccines indicated for immunization against pertussis are as follows[47]: Adacel[48], Boostrix[49], Daptacel[50], Infanrix[51], Kinrix[52], Pediarix[53], Pentacel[54], Quadracel[55], and Vaxelis[56].

## III. DISCUSSION: THE PETITION'S REQUEST TO AMEND PERTUSSIS VACCINE LABELING

The Petition requests that FDA require "all manufacturers of acellular pertussis-containing vaccines … to amend the package inserts of these products to disclose that they do not prevent infection and transmission of pertussis."[57]

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[41] CDC, Chp. 16: Pertussis, The Pink Book, at 245.
[42] Id.
[43] Id.
[44] *See* "Description" sections of the Prescribing Information for vaccines containing an acellular pertussis component.
[45] CDC, Chp. 16: Pertussis, The Pink Book, at 245.
[46] CDC, Pertussis (Whooping Cough), last reviewed August 2022, https://www.cdc.gov/pertussis/about/prevention/index.html.
[47] All vaccines currently approved by FDA for immunization against pertussis contain tetanus toxoid and diphtheria toxoid and are also indicated for immunization against diphtheria and tetanus.
[48] See FDA, Vaccines, Blood & Biologics-Adacel, https://www.fda.gov/vaccines-blood-biologics/vaccines/adacel.
[49] See FDA, Vaccines, Blood & Biologics-Boostrix, https://www.fda.gov/vaccines-blood-biologics/vaccines/boostrix.
[50] See FDA, Vaccines, Blood & Biologics-Daptacel, https://www.fda.gov/vaccines-blood-biologics/vaccines/daptacel.
[51] See FDA, Vaccines, Blood & Biologics-Infanrix, https://www.fda.gov/vaccines-blood-biologics/vaccines/infanrix.
[52] See FDA, Vaccines, Blood & Biologics-Kinrix, https://www.fda.gov/vaccines-blood-biologics/vaccines/kinrix.
[53] See FDA, Vaccines, Blood & Biologics-Pediarix, https://www.fda.gov/vaccines-blood-biologics/vaccines/pediarix.
[54] See FDA, Vaccines, Blood & Biologics-Pentacel, https://www.fda.gov/vaccines-blood-biologics/vaccines/pentacel.
[55] See FDA, Vaccines, Blood & Biologics-Quadracel, https://www.fda.gov/vaccines-blood-biologics/vaccines/quadracel.
[56] See FDA, Vaccines, Blood & Biologics-Vaxelis, https://www.fda.gov/vaccines-blood-biologics/vaxelis.
[57] Petition at 1.

Petitioner states that "[i]ndividuals receiving [acellular pertussis] vaccines may be protected from symptoms resulting from pertussis, but these vaccines do not prevent infection and transmission of pertussis"[58] and "individuals administered [acellular pertussis] vaccines can still become infected with and transmit pertussis while remaining asymptomatic or paucisymptomatic."[59, 60] Additionally, Petitioner claims that "a grandmother who received an [acellular pertussis] vaccine and was exposed to someone with pertussis may assume that she is not susceptible to infection and cannot transmit pertussis to her grandchild because she received this product."[61] Petitioner asserts that consumers "should be informed in the package insert of all [acellular pertussis] vaccines that *while this product may reduce their symptoms, it does not prevent them from becoming infected with and transmitting pertussis*."[62]

Your Petition does not persuade us that a revision to the labeling is needed. As discussed further in the paragraphs that follow, your proposed labeling revision is not required by statute or regulation and we are not convinced by your arguments that the change is necessary for the safe and effective use of the vaccines.

It is important to note that FDA's licensure standards for vaccines do not require demonstration of the prevention of infection or transmission. A vaccine can meet the licensure standard if the vaccine's benefits of protecting against disease outweigh the vaccine's risks for the licensed use. There is no requirement that the vaccine also prevents infection with the pathogen that can cause the disease or transmission of that pathogen to others.

After undergoing a rigorous and comprehensive scientific and regulatory process to demonstrate that the relevant statutory and regulatory requirements are satisfied, the licensed acellular pertussis vaccines have been licensed for active immunization against pertussis. Indeed, the pertussis vaccines that FDA has licensed are for prevention of pertussis disease[63] not infection with *B. pertussis*. Pertussis disease occurs after infection and colonization of the respiratory tract by *B. pertussis*. Vaccines work by mimicking the infectious bacteria or viruses that cause

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[58] Id. at 2.
[59] Id. at 3.
[60] Additionally, we note that Petitioner states that "pertussis can cause serious illness in newborns and infants" but claims that "[p]ertussis in adults is generally mild and can, if necessary, be treated with antibiotics." Petition at 2. As discussed above in section II.C, pertussis is a serious disease that can affect individuals of all ages and is especially serious for young infants and children. According to the CDC, medical management of pertussis patients is primarily supportive, although antibiotics are of some value if administered early. (*see* CDC, Chp. 16: Pertussis, The Pink Book, at 242). Additionally, CDC recommendations provide that "[e]arly treatment of pertussis is most effective for reducing symptom severity… [a]ntibiotics will not alter the course of the illness or prevent transmission if they are given later in the course of illness." (CDC, Pertussis (Whooping Cough): Treatment, last reviewed August 2022, https://www.cdc.gov/pertussis/clinical/treatment.html). The Petition provides no information indicating that the benefits of currently licensed pertussis vaccines for the prevention of pertussis do not generally outweigh the risks. (See 21 CFR 201.57(c)(2)(ii) ("If…the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.").
[61] Petition at 3.
[62] Id. (Emphasis in original).
[63] FDA regulation, 21 CFR 101.14(a)(5), defines disease as "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension)[.]" Note that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition. Id.

disease.[64] Vaccination stimulates the body's immune system to build up defenses against the infectious bacteria or virus (organism) without causing the disease.[65] The parts of the infectious organism that the immune system recognizes are foreign to the body and are called antigens.[66] Vaccination exposes the body to these antigens.[67] After vaccination, the immune system is prepared to respond quickly and forcefully when the body encounters the real disease-causing organism.[68] Adolescents, adults, and children who were previously vaccinated against pertussis may become infected with *B. pertussis* but may have milder disease.[69]

Importantly, the approved Prescribing Information for the licensed vaccines containing an acellular pertussis component is consistent with the applicable statutory and regulatory requirements in that they accurately describe the approved indications. As required by FDA regulations, the Prescribing Information of currently licensed vaccines containing an acellular pertussis component accurately describe the approved indication(s) of these vaccines and present data related to this indication.[70] For each of the currently licensed vaccines containing an acellular pertussis component, the Indications and Usage section of the Prescribing Information presents the vaccine's indication (active immunization against pertussis) and data to support these indications are described in the Clinical Studies section.[71] The current labeling therefore clearly sets forth the approved use.

The Petition's request is supported by assertions about what vaccinated individuals may believe about the protection afforded by vaccination. However, assertions regarding what some vaccinated individuals may believe is not evidence that there is any widespread misconception about the protection provided by vaccines. In addition, Petitioner references an article published in the journal *Frontiers in Immunology: Vaccines and Molecular Therapeutics* stating that "[acellular] pertussis vaccines do not prevent colonization … do not reduce the circulation of B. pertussis and do not exert any herd immunity effect."[72] The article cited by Petitioner discusses various reasons for increases in reported pertussis cases over the past few decades.[73] But the

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[64] FDA, Vaccine Development – 101, last updated December 2020, https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101.
[65] Id.
[66] Id.
[67] Id.
[68] Id.
[69] CDC, Chp. 16: Pertussis, The Pink Book at 240.
[70] See 21 CFR 201.57(c)(2).
[71] See e.g. Adacel-Package Insert, https://www.fda.gov/media/119862/download.; Boostrix-Package Insert, https://www.fda.gov/media/124002/download.; Daptacel-Package Insert, https://www.fda.gov/media/74035/download.; Infanrix-Package Insert, https://www.fda.gov/media/75157/download.; Kinrix-Package Insert, https://www.fda.gov/media/80128/download.; Pediarix-Package Insert, https://www.fda.gov/media/79830/download.; Pentacel-Package Insert, https://www.fda.gov/media/74385/download.; Quadracel-Package Insert, https://www.fda.gov/media/91640/download.; Vaxelis-Package Insert, https://www.fda.gov/media/119465/download.
[72] Petition at 2 (citing Esposito, et. al., Pertussis Prevention: Reasons for Resurgence, and Differences in the Current Acellular Pertussis Vaccines, 10 Front. Immunol. (Article1344) (July 3, 2019), at 5, https://www.frontiersin.org/articles/10.3389/fimmu.2019.01344/full).
[73] Reported pertussis cases have increased gradually over the past few decades, and by 2019 more than 18,000 cases were reported nationwide. (CDC, Pertussis (Whooping Cough): Surveillance and Reporting, last reviewed August

article does not provide any evidence that would support a conclusion that there is a commonly held belief that vaccines containing an acellular pertussis component prevent infection and transmission of pertussis. Petitioner also references a study published in the *Proceedings of the National Academy of Sciences of the United States of America*[74] and an article published in *Vaccine*.[75] The study referenced by Petitioner was an FDA study examining colonization and transmission of pertussis in baboon subjects following vaccination with both whole and acellular pertussis vaccines.[76] The findings of this study suggested that while acellular pertussis vaccines provide protection against disease and are sufficient for preventing severe pertussis symptoms, acellular pertussis vaccines do not prevent pertussis infection or transmission; however, "any short-term plan for addressing the resurgence of pertussis should include continued efforts to enhance [acellular pertussis] immunization."[77] This study does not provide any evidence that there is a common belief that vaccines containing an acellular pertussis component are effective for a certain use but a preponderance of scientific evidence provides otherwise. Likewise, the *Vaccine* article referenced by Petitioner does not provide any evidence that there is a common belief that these vaccines prevent infection. Rather, the article discusses several strategies to address rises in pertussis cases, including the development of new vaccines.[78, 79] In short, the Petition has not provided evidence of any widespread misconception about the effectiveness of licensed vaccines containing an acellular pertussis component with respect to preventing infection and transmission of pertussis, nor are we convinced that there is any widespread misconception about this.

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2022, https://www.cdc.gov/pertussis/surv-reporting.html). The CDC has stated that there are a number of likely factors contributing to this observed increase in reported cases, these factors include: changes in diagnostic testing, heightened recognition and reporting of pertussis cases, molecular changes in the organism, and possible waning of vaccine-induced immunity. (CDC, Chp. 16: Pertussis, The Pink Book, at 244). The exact causes for resurgence in observed pertussis cases are not entirely understood. Petitioner states that "individuals may have few or no symptoms if infected with pertussis *but* will still become colonized with and silently transmit pertussis." Petition at 3. Petitioner characterizes this as "defective immunity [which] remains…after an individual receiving aP vaccines becomes infected with pertussis virus." Id. Clinical research, including FDA research, is ongoing and the scientific community has not reached a consensus as to the reason for increases in reported pertussis cases.

[74] Petition at 2 (citing Warfel, et al., Acellular Pertussis Vaccines Protect Against Disease but Fail to Prevent Infection and Transmission in a Nonhuman Primate Model, 111 Proc Natl Acad Sci USA 787, (Jan. 14, 2014), Epub Nov. 25, 2013. https://pubmed.ncbi.nlm.nih.gov/24277828/).

[75] Petition at 2 (citing Locht, Will We Have New Pertussis Vaccines?, 36 Vaccine 5460, (Aug. 28, 2018), https://pubmed.ncbi.nlm.nih.gov/29180031/).

[76] Warfel, et al., Acellular Pertussis Vaccines Protect Against Disease but Fail to Prevent Infection and Transmission in a Nonhuman Primate Model, at 787.

[77] Id. at 791.

[78] *See* Locht, Will We Have New Pertussis Vaccines?, at 5462-5467.

[79] Additionally, all three publications referenced by Petitioner note CDC recommendations for pertussis vaccination. At the onset, we note that FDA approves vaccines and their labeling, but does not make recommendations regarding the use of vaccines. The federal entity responsible for issuing recommendations on the use and timing of vaccines is the CDC (*See* CDC, Vaccines for Your Children: Who Sets the Immunization Schedule?, last reviewed February 2021, https://www.cdc.gov/vaccines/parents/schedules/sets-schedule.html ("CDC sets the immunization schedules based on [the Advisory Committee on Immunization Practices's] recommendations.")). The CDC recommends pertussis vaccination. (*See* CDC, Pertussis (Whooping Cough): Whooping Cough Vaccination, last reviewed August 2022, https://www.cdc.gov/pertussis/vaccines.html). We note that the Petition makes no claim that the CDC's recommendations and statements related to pertussis vaccination provide any evidence that the vaccine labeling is misleading or otherwise unlawful with respect to pertussis infection or transmission.

For all of the above-described reasons, we deny the request for FDA to require "all manufacturers of acellular pertussis-containing vaccines … to amend the package inserts of these products to disclose that they do not prevent infection and transmission of pertussis."

## IV. CONCLUSION

FDA has considered Petitioner's requests as they relate to the labeling of vaccines containing an acellular pertussis component. Based on our review and consideration of these requests, FDA has determined that requiring manufacturers of these vaccines to amend their package inserts as requested by the Petition is unwarranted. Therefore, for the reasons given in this letter, FDA denies the Petition in its entirety.

Sincerely yours,

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff