Clinical Evaluation of Pertussis Vaccines: US Food and Drug Administration Regulatory Considerations

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The resurgence of pertussis in the United States has stimulated considerable public health interest in developing new vaccination strategies to improve control of pertussis. The purpose of this article is to review the US Food and Drug Administration’s regulatory framework for the prelicensure clinical evaluation of preventive vaccines and the clinical approaches that have been used to demonstrate effectiveness of US-licensed vaccines containing an acellular pertussis component.

Keywords. pertussis vaccines; regulatory pathways; vaccine effectiveness.

In this article, we review the regulatory framework used by the US Food and Drug Administration (FDA) for prelicensure clinical effectiveness evaluation of preventive vaccines, with a focus on vaccines that contain an acellular pertussis component.

REGULATORY FRAMEWORK FOR PRELICENSURE CLINICAL EVALUATION OF PREVENTIVE VACCINES


Vaccines licensed by the FDA must be safe, pure, and potent. Extensive laboratory characterization of biologic materials used in vaccine production is essential to assure purity. Review of manufacturing processes, product testing, animal studies, clinical trials, and post-licensure surveillance contribute to the evaluation of safety and potency. The FDA defines safety as the relative freedom from harmful effects to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product and the condition of the recipient [1]. Thus, specific requirements for the clinical safety evaluation of preventive vaccines depend on characteristics of the vaccine, the target population, and the disease to be prevented. The FDA interprets potency to include effectiveness [2]. All approved indications for preventive vaccines must be supported by substantial evidence of effectiveness [3]. This article focuses on the prelicensure clinical evaluation of vaccine effectiveness.

In general, for preventive vaccines, the FDA expects that the demonstration of effectiveness is based on adequate and well-controlled clinical studies. Characteristics of adequate and well-controlled clinical studies include a clear statement of objectives and analysis methods; a design that permits a valid comparison with a control to provide a quantitative assessment of effect; methods of assigning participants to study groups that minimize bias and help assure comparability of groups with regard to pertinent variables; measures to minimize bias on the part of participants, observers, and data analysts; and methods to assess response that are prespecified, well defined, and reliable [4]. The scientific community recognizes these characteristics as important to permit a valid evaluation of vaccine effect.
The FDA expects the clinical evaluation of candidate vaccines to include concomitant administration with licensed vaccines recommended for routine use in the same population on the same, or overlapping, schedule. Potential interference of the candidate vaccine with the immune response to concomitantly administered vaccines should be evaluated.

Vaccines to prevent infectious diseases have been licensed in the United States through 2 licensure pathways, “traditional” approval and accelerated approval. Although prelicensure clinical evaluation of safety and effectiveness is always required, approaches to demonstrate effectiveness differ for the 2 pathways. For traditional approval of preventive vaccines, effectiveness is primarily based either on a demonstration of efficacy in preventing clinical disease, or in some cases, on immunologic response. Often, both clinical efficacy data and immunologic response data contribute to the evaluation of vaccine effectiveness. In general, for a disease such as tetanus or diphtheria, for which there is a scientifically well-established immunologic marker that predicts protection and that can be reliably measured in a validated assay, immunologic response data provide sufficient evidence of effectiveness, without the need for clinical end point efficacy studies. In contrast, pertussis immunologic response data alone have not been considered sufficient evidence of vaccine effectiveness to support traditional approval because there is no scientifically well-established immunologic marker that predicts protection against pertussis. The basis for effectiveness of US-licensed acellular pertussis-containing vaccines, all of which were approved by the traditional licensure pathway, will be discussed in the next section.

Accelerated approval may be granted for certain biologic products that have been studied for safety and effectiveness in treating serious illnesses and that provide meaningful therapeutic benefit over existing treatments [5]. Such approval is based on adequate and well-controlled clinical trials establishing an effect on a surrogate end point that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit [5]. For example, end points based on hemagglutination inhibition antibody have been used to support accelerated approval of some influenza vaccines [6]. Accelerated approval based on such surrogate end points is subject to the requirement that the sponsor study the product further to verify the anticipated clinical benefit. These required postmarketing studies, usually underway at the time of approval, must be adequate and well controlled. Approval by this pathway may be withdrawn, for example, if the postmarketing clinical study fails to verify clinical benefit [5].

PRELICENSURE EFFECTIVENESS EVALUATION OF PERTUSSIS VACCINES LICENSED IN THE UNITED STATES

Rationale for Approach
Unlike whole-cell pertussis vaccines, which contain suspensions of killed Bordetella pertussis organisms, less reactogenic acellular pertussis vaccines comprise ≥1 purified antigens that play a role in pertussis pathogenesis. Pertussis toxin (inactivated), filamentous hemagglutinin, pertactin, and fimbriae induce antibodies that contribute to protection in an animal model, and natural infection with B. pertussis in humans induces antibodies to each of these antigens [7]. However, there is no scientifically well-established immunologic marker of protection for pertussis. The protective mechanism of the vaccines, probably multifactorial, has not been fully elucidated.

Acellular pertussis-containing vaccines that have been licensed in the United States include diphtheria and tetanus toxoids and acellular pertussis, adsorbed (DTaP); DTaP-based combination; and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) vaccines (Table 1). Some of these vaccines contain the same pertussis antigens produced by the same manufacturer and methods. Such vaccines may be considered “linked” with regard to their pertussis components. In contrast, the acellular pertussis components of vaccines from different manufacturers may differ in several respects, including number of pertussis antigens, source of antigens, toxin inactivation methods, and antigen purification methods.

As described in more detail below, the distinction between linked acellular pertussis-containing vaccines and those from different manufacturers is important to the approach used to evaluate vaccine effectiveness. For example, the FDA has accepted comparisons of pertussis antibody responses between a DTaP vaccine shown to be efficacious in a pertussis clinical end point efficacy trial and other linked acellular pertussis-containing vaccines from the same manufacturer. In contrast, because of the many differences in acellular pertussis components of vaccines from different manufacturers that may affect vaccine-induced protection and because pertussis antibody assays are not fully standardized, it would not be meaningful to compare pertussis antibody responses elicited by such vaccines.

DTaP Vaccines
Table 1 lists DTaP vaccines that have been licensed in the United States for use in infants and children aged 6 weeks to 7 years. Each of these vaccines was evaluated for efficacy in preventing pertussis when administered to infants in ≥1 of the controlled clinical trials conducted in the early 1990s in European countries with low rates of pertussis vaccination and a high incidence of pertussis. The studies differed in several respects, including design, population, vaccination schedule, control vaccines, surveillance methods, and case definitions.

Each of these DTaP vaccines was efficacious in preventing pertussis, using a case definition developed by an expert group convened in 1991 by the World Health Organization [8], or a closely related definition. The pertussis case definition developed at the World Health Organization meeting requires the presence of paroxysmal cough for ≥21 days plus ≥1 of the following: positive culture for B. pertussis, serologic evidence of
Bordetella-specific infection by a significant rise in specified antibodies, or household contact with a *B. pertussis* bacteriologically confirmed case occurring within 28 days before or after onset of illness [8]. In most studies, efficacy was evaluated approximately 1–2 years after receipt of the third dose of DTaP vaccine.

To provide assurance that a particular DTaP vaccine would also be effective in US infants, seroresponse rates and geometric mean titers of antibodies to each of the pertussis antigens in the vaccine, measured with the same assays, were compared between infants in a US study and those in the efficacy study using prespecified criteria. In some cases, these immunogenicity comparisons also bridged different vaccination schedules.

**DTaP-Based Combination Vaccines**

Some DTaP vaccine manufacturers developed vaccines consisting of a DTaP component combined with ≥1 other antigens. For each of the US-licensed DTaP-based combination vaccines, the linked licensed DTaP vaccine containing the same pertussis antigens produced by the same manufacturer and process had been shown to be efficacious in preventing pertussis in a clinical end point efficacy study (or studies). In subsequent randomized clinical trials, the safety and immunogenicity of each DTaP-based combination vaccine were evaluated relative to separately administered control vaccines, including the relevant DTaP vaccine. Consistent with current regulatory expectations, in most of these trials, prespecified criteria were used to evaluate whether antibody responses to each of the pertussis antigens in recipients of the DTaP-based combination vaccine were noninferior to those in recipients of the control DTaP vaccine. Along with the clinical end point, pertussis efficacy data on the linked DTaP vaccine, data from these comparative immunogenicity analyses supported the effectiveness of the pertussis component of the DTaP-based combination vaccine.

### Table 1. Acellular Pertussis–Containing Vaccines Licensed in the United States

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Trade Name</th>
<th>Manufacturera</th>
<th>Pertussis Antigensb</th>
<th>Other Antigensb</th>
<th>“Linked” DTaP Vaccinec</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP vaccines</td>
<td>Acel-Imune®</td>
<td>Lederle</td>
<td>PT, FHA, PRN, FIM2</td>
<td>D, T</td>
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<tr>
<td></td>
<td>Certiva®</td>
<td>North American Vaccine, Inc</td>
<td>PT</td>
<td>D, T</td>
<td>. . .</td>
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<tr>
<td></td>
<td>Daptacel</td>
<td>Sanofi Pasteur Ltd</td>
<td>PT, FHA, PRN, FIM2/3</td>
<td>D, T</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td>Infanrix</td>
<td>GlaxoSmithKline Biologicals and Novartis Vaccines and Diagnostics GmbH</td>
<td>PT, FHA, PRN</td>
<td>D, T</td>
<td>. . .</td>
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<tr>
<td></td>
<td>Tripedia</td>
<td>Sanofi Pasteur Inc</td>
<td>PT, FHA</td>
<td>D, T</td>
<td>Infanrix</td>
</tr>
<tr>
<td>DTaP-based combination vaccines</td>
<td>Kinrix</td>
<td>GlaxoSmithKline Biologicals and Novartis Vaccines and Diagnostics GmbH</td>
<td>PT, FHA, PRN</td>
<td>D, T, IPV</td>
<td>Edanrix</td>
</tr>
<tr>
<td></td>
<td>Pediarix</td>
<td>GlaxoSmithKline Biologicals and Novartis Vaccines and Diagnostics GmbH</td>
<td>PT, FHA, PRN</td>
<td>D, T, HBsAg, IPV</td>
<td>Infanrix</td>
</tr>
<tr>
<td></td>
<td>Pentacel</td>
<td>Sanofi Pasteur Ltd and Sanofi Pasteur SA</td>
<td>PT, FHA, PRN, FIM2/3</td>
<td>D, T, PRP, IPV</td>
<td>Daptacel</td>
</tr>
<tr>
<td></td>
<td>TriHibit</td>
<td>Sanofi Pasteur Inc and Sanofi Pasteur SA</td>
<td>PT, FHA</td>
<td>D, T, PRP</td>
<td>Tripedia</td>
</tr>
<tr>
<td>Tdap vaccines</td>
<td>Adacel</td>
<td>Sanofi Pasteur Ltd</td>
<td>PT, FHA, PRN, FIM2/3</td>
<td>d, T</td>
<td>Daptacel</td>
</tr>
<tr>
<td></td>
<td>Boostrix</td>
<td>GlaxoSmithKline Biologicals and Novartis Vaccines and Diagnostics GmbH</td>
<td>PT, FHA, PRN</td>
<td>d, T</td>
<td>Infanrix</td>
</tr>
</tbody>
</table>

Abbreviations: D and d, diphtheria toxoid (with d indicating relatively lower amount than D); DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed; FHA, filamentous hemagglutinin; FIM, fimbrial proteins; HBsAg, hepatitis B surface antigen; IPV, inactivated poliovirus types 1, 2, and 3; PRN, pertactin; PRP, *Haemophilus influenzae* type b capsular polysaccharide polyribosyl-ribitol-phosphate; PT, inactivated pertussis toxin; T, tetanus toxoid; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed.

a For vaccines currently licensed in the United States, manufacturer names are listed according to current approved prescribing information. For vaccines no longer licensed in the United States, the original manufacturer names are listed according to previously approved prescribing information.

b Antigens listed for different vaccines may differ with regard to amount and/or manufacturing procedures.

c A “linked” DTaP vaccine is a DTaP vaccine containing the same pertussis antigens produced by the same manufacturer and methods as that of the specified DTaP-based combination vaccine or Tdap vaccine.

d No longer licensed in the United States at the request of the manufacturer.
Tdap Vaccines

In response to the disproportionately large increase of reported pertussis among US adolescents and adults since the 1980s [9, 10], 2 manufacturers developed Tdap vaccines for use in these age groups. The acellular pertussis component of each licensed Tdap vaccine is the same as that of the licensed DTaP vaccine from the same manufacturer, with the exception of a reduced quantity of ≥1 of the pertussis antigens. For approval of these Tdap vaccines, the FDA did not require clinical end point efficacy data on the prevention of pertussis in adolescents and adults. The efficacy of the linked DTaP vaccine in preventing pertussis in infants supported the effectiveness of the pertussis component of the Tdap vaccine.

In addition, the safety and immunogenicity of each Tdap vaccine were evaluated in randomized clinical trials in which adolescents and adults received 1 dose of Tdap vaccine or a US-licensed tetanus and diphtheria toxoids, adsorbed, vaccine. With use of prespecified criteria and the same assays, postvaccination geometric mean titers of antibodies to each of the pertussis antigens contained in the vaccines were evaluated in Tdap-vaccinated adolescents and adults relative to infants who had received a primary series with the linked DTaP vaccine in an earlier efficacy trial. Based on prespecified definitions and success criteria, the proportion of Tdap-vaccinated adolescents and adults who demonstrated a booster response to each of the pertussis antigens was also determined. Along with the clinical end point, pertussis efficacy data on the linked DTaP vaccine, these immunogenicity data supported the effectiveness of the pertussis component of the Tdap vaccines.

FUTURE CLINICAL EVALUATION OF PERTUSSIS VACCINES

US postmarketing effectiveness data corroborate prelicensure efficacy estimates for DTaP vaccines with regard to prevention of pertussis in the relative short term. However, national pertussis surveillance data and findings from postmarketing effectiveness studies are consistent with a progressive decrease in vaccine effectiveness with each year after the fifth dose of DTaP vaccine [11–13] and suggest relatively early waning of protection after the adolescent dose of Tdap vaccine [14]. Potential strategies to improve control of pertussis that were discussed at the Working Group Meeting on Pertussis held in Bethesda, Maryland, on 6 March 2013, include changes in vaccination schedules using already licensed pertussis vaccines, development of acellular pertussis-only vaccines for additional doses, and development of new vaccines that might confer longer lasting protection.

Regulatory pathways exist for approval of new vaccines and new dosing regimens for licensed vaccines. Before licensure of new vaccines, legal regulatory requirements for demonstration of purity, safety and potency, including effectiveness, must be met. Specific requirements for clinical safety and effectiveness data for new preventive vaccines depend on the characteristics of the vaccine and its intended use. Principles underlying previous regulatory use of pertussis immunogenicity data to support vaccine effectiveness potentially may be applicable to other vaccines, such as acellular pertussis vaccines, which differ from the same manufacturer’s licensed Tdap vaccine only in the absence of tetanus and diphtheria toxoids. Although demonstration of effectiveness for new pertussis vaccines may be challenging, the approach taken must have a clear scientific basis. Advances in the scientific understanding of pertussis pathogenesis and host protective mechanisms are needed to facilitate development and clinical evaluation of improved pertussis vaccines.

Notes

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3. Code of Federal Regulations. 21 CFR §201.57. Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).