Prelicensure Evaluation of Combination Vaccines

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There is considerable public health interest in licensing safe and effective combination vaccines. Because combination vaccines may progress rapidly from phase 1 to a pivotal phase 2 immunogenicity trial, a rigorous approach to address product issues early in development is warranted. Clinical studies to evaluate the safety, immunogenicity, and (when necessary) clinical end point efficacy of combination vaccines should be randomized and well controlled in most cases. A large phase 3 safety study (i.e., a study that enrolls thousands of vaccinees) should be included in the development plan if a phase 3 (clinical end point) efficacy trial will not be conducted. Often, the new combination vaccine under development contains immunogens that have all been previously licensed, have demonstrated efficacy in earlier clinical trials, or both. For such products, comparative immunogenicity data may be sufficient to support efficacy. When applicable, clinical data to support simultaneous administration with other relevant vaccines should be obtained. Given the complexity of combination vaccine development, early consultation with United States Food and Drug Administration can be invaluable.
products and manufacturing

**General considerations.** With regard to manufacturing, product, and establishment topics, emphasis is placed on 2 FDA guidance documents, one of which addresses combination vaccines [7] and the other of which addresses chemistry, manufacturing, and control information for vaccines [20]. We also refer readers to the article by Falk et al. [21] in this issue for a more detailed discussion of product and manufacturing issues.

Detailed information concerning the source and quality of starting materials, characterization of seed stocks, adventitious agent testing, performance of manufacturing steps and process controls, potency, general safety, purity, and identity of the final product should be documented. Adequate manufacturing methods and production controls are important in establishing the safety and biologic activity of the product, as well as the consistency of the manufacturing process [22].

**Special issues for combination vaccines.** The FDA recognizes that manufacturing refinements and improvements in testing methods often occur during product development. Thus, the extent of documentation required by FDA with regard to manufacturing procedures will increase as clinical studies progress. However, critical areas, such as a clear description of manufacturing, as well as adventitious agent testing, should be addressed in the original investigational new drug application (IND) in a manner that allows an adequate review of product safety to be performed. Combination vaccines can have a rapid progression from phase 1 to a pivotal phase 2 immunogenicity trial, which will necessitate a rigorous approach to address product and manufacturing issues early in development.

Descriptions of manufacturing and product controls are needed for each component of the combination vaccine. Changes in one component of the combination vaccine have the potential to affect the safety and effectiveness of the final product. Therefore, when combining antigens, it may be nec-
essary to reevaluate the acceptability of tests being used preclinically for any component of the vaccine. The same applies to the reevaluation of final release testing for each component as additional antigens are added to the multicomponent vaccine. Evaluation of combination vaccines also includes determining the effects of excipients, adjuvants, and preservatives used in the manufacture of intermediate bulk antigens or added to the formulation of the final product on the potency of each antigen in the final combination product [3, 4, 7, 23, 24].

**Manufacturing.** The manufacturer should document the source and quality of all materials used in the manufacture of the vaccine. Detailed descriptions of the characterization of bacterial and viral master seeds, as well as working seed stocks, should be provided. In this regard, important topics to cover include isolation, passage history, and growth characteristics. When seeds that have been modified by recombinant DNA technology are used, it is important to include information about the stability of the construct [25, 26]. In the case of viral vaccines, cell substrate issues should be addressed [27, 28]. When applicable, the methods of attenuation, inactivation, or detoxification should be adequately described and supported with appropriate validation data [7, 20].

**Final formulation.** A potency test for each vaccine antigen in the final product should be established. Potency can be viewed as the ability of a vaccine to effect a given result through either the use of laboratory tests or by controlled clinical data [29]. Quantitative potency tests are generally considered necessary to assess the biological activity of each active component of a combination vaccine and can also serve as an important measure of product stability. A variety of potency assays may be acceptable. For example, potency tests may represent a serological evaluation or challenge test after vaccination of animals or may rely on physiochemical characterization, such as composition and molecular weight (e.g., certain polysaccharide vaccines). Identity testing on the labeled final container may include immunological assays for vaccine antigens and serotyping of vaccine organism strains [6]. In addition, results of tests for product sterility and the absence of toxicity from extraneous contaminants (i.e., General Safety Test) should be provided.

**Stability.** Product stability testing is essential for selecting an appropriate dating period for expiration, as well as for future extensions of the dating period. In most cases, stability parameters (e.g., potency and sterility) are evaluated by use of real-time data under ideal conditions of storage [30]. Stability protocols that specify which tests are to be performed at predetermined intervals should be initiated early in product development (and shared with the FDA). Stability studies are needed for each presentation of the final product (e.g., single and multidose vials and prefilled syringes).

**CLINICAL EVALUATION**

**Overview.** The focus here will be on the phase 1, 2, and 3 clinical studies of combination vaccines. Assuming that the new vaccine appears to be safe and effective, the results of these studies can be submitted in a biologics license application to support approval for marketing in the United States [31].

We refer the reader to the section on “adequate and well-controlled studies” in the Code of Federal Regulations for a discussion of the choice of control groups and study design [32]. Clinical studies to evaluate the safety, immunogenicity, and (clinical end point) efficacy of combination vaccines should be randomized and well controlled, in most cases [6, 7, 33–35].

In contrast, comparisons with historical data, as opposed to a randomized control group, have well-recognized limitations [6, 7, 32]. In the case of vaccines, interpretation of results may be confounded by such things as differences between populations, immunization time frame, simultaneously administered vaccines, antipyretic use (prophylactic, therapeutic, or both), safety or efficacy case definitions, and surveillance methodology [6, 7, 35]. Also, there are clear examples where the background rate of an adverse event is not uniform during the first year or so of life—for example, sudden infant death syndrome. In this example, comparisons with historical cohorts without month of age adjustments would obviously be misleading due to this factor alone.

Well-designed case report forms (to assess safety, efficacy, etc.) and scripted interviews for any protocol-specified telephone follow-up are critical for obtaining meaningful data. These model forms and documents should be submitted to the IND at the same time as the protocol.

Results from the clinical trials provide the basis for the clinical sections of the package insert. Although the most intensive work on the package insert occurs several months before approval, clinical development plans should anticipate expected claims and information to be included in the label. For example, safety and immunogenicity data on the simultaneous use of a new vaccine with other routinely administered licensed vaccines is an important component of the package insert. Also, when applicable, plans to obtain data on booster doses and “catch-up” age groups should be implemented as early as is feasible during clinical development. Prelicensure vaccine clinical trials often exclude premature infants, immunocompromised populations, and other special populations. If there is likely to be interest in postlicensure use of a vaccine in such populations, sponsors are urged to plan trials to address safety and immunogenicity (and clinical end point efficacy, if applicable) in these populations during clinical development.
SAFETY

Obtaining an adequate safety database to support licensure is a critical objective for the clinical development plan for a new combination vaccine. In designing studies to meet this objective, emphasis is placed on the size of the potential target population for most pediatric combination vaccines—that is, the birth cohort in the United States of approximately 4 million. The most relevant safety data are from studies that use the product at the dose, schedule, formulation, and route of administration intended for licensure.

Often, the new combination vaccine under development only contains immunogen components with already proven efficacy (which is assessed on the basis of previous trials with clinical end points). Thus, for such new combination vaccines, comparative immunogenicity data from studies with sample sizes of several hundred participants, at most, per group may provide a sufficient basis to support efficacy [3, 6, 7]. However, with this type of development plan, the extensive clinical safety database obtained from a phase 3 well-controlled clinical end point efficacy trial(s) will not be available. Thus, an additional prelicensure trial should be conducted to obtain an adequate safety database to support the safety of a new combination vaccine [3].

Phase 2 and 3 clinical trials to evaluate safety should be randomized and well controlled. Typically, people in the control group receive the separate, simultaneously administered components (or currently licensed combinations of components) contained in the new combination vaccine, as appropriate [6, 7, 35]. For example, in the evaluation of a new DTaP and hepatitis B (Hep B) combination vaccine, the control group may receive separate injections of currently licensed DTaP and Hep B vaccines. However, as more combination products are licensed, these comparisons may become increasingly difficult to perform. Thus, there are also situations where the safety of a new combination vaccine may be compared with a different manufacturer’s licensed combination of the same immunogens, especially for phase 3 safety studies.

Adequate monitoring of subjects for adverse events is an important component of prelicensure studies [7]. Thus, a satisfactory, well-documented monitoring system must be in place to detect and record the events of interest throughout the study. Solicited adverse events should be graded for severity by use of standardized definitions for severity (ideally, definitions that the sponsor uses across studies for that product). (It is of note that case report forms for all serious adverse events would be submitted as part of a future license application.)

Phase 2 trials can provide well-controlled data on common injection site reactions and systemic events (as well as immunogenicity data) for the combination vaccine compared with the control vaccine. In some cases, the phase 2 data may also provide information regarding specific adverse events that should be evaluated more carefully in a larger phase 3 trial. To increase the total prelicensure population exposure, a larger phase 3 safety trial with a sample size adequate to evaluate less common adverse events is performed. For such larger trials (i.e., those that enroll thousands of vaccinees), a simplified design may be acceptable where only a subset of subjects in each group is assessed in detail for the more-common events [7]. Also, unequal allocation ratios (e.g., 3:1 or 2:1, with more people in the new combination vaccine group) could be considered [6, 7, 35].

Sometimes sponsors have tried to address the need for safety data in thousands of people through the use of several small safety studies. However, data from a single phase 3 multicenter safety study that used a single clinical protocol with consistent and well-defined surveillance methods, adverse event severity definitions, and appropriate control group are more readily reviewed, interpreted, and described in the label than data from multiple, smaller safety studies without such documented consistency [6, 7, 35].

Usually, the goal of comparative safety studies is to demonstrate similarity of the safety profile between the combination vaccine and the separately administered components. It has been suggested that these equivalence (noninferiority) trials be designed and analyzed to reject a hypothesis of a specified difference, rather than the traditional null hypothesis of no difference [36].

The selection of less common but important events for evaluation in a larger comparative safety study can be based on a consideration of the events observed in the available studies of the new combination vaccine, its separate components, and similar licensed products, if applicable. When assessing reactogenicity, point estimates and 95% confidence intervals should be provided for adverse event rates; this applies to both within and between comparator groups. In addition, confidence intervals on the difference between the new combination vaccine and the separate components should accompany formal hypothesis tests—and in fact may compose the primary analysis. There is often interest in interpreting the finding that a certain event did not occur in a trial of a certain size (n). In this regard, the “rule of 3” can be used to provide a 95% confidence interval (0, 3/n) for the true event rate [37].

The finding that a combination vaccine has a high rate of common local or systemic events than the separate components does not by itself preclude the possibility of licensure. Such findings would need to be considered in the risk-benefit assessment of a product. Also, even with the size of phase 3 trials, postlicensure studies may be needed to assess the potential for rare but serious events [38–40]. Ideally, consensus between FDA and sponsors with regard to postlicensure studies should be reached before license application approval.
IMMUNOGENICITY

Efficacy of new vaccines is usually assessed in clinical end point trials demonstrating prevention of an infectious disease. However, for new combination vaccines with components consisting of previously licensed products or antigens for which efficacy has already been demonstrated in clinical trials, serological immune response end points may be adequate to substantiate efficacy for licensure. As with pivotal clinical end point efficacy trials, more than 1 pivotal immunogenicity study may be necessary if the results are not compelling [41].

The immune responses elicited by new combination vaccines are ordinarily evaluated in randomized, well-controlled studies. Specifically, the immune responses to the respective antigens in 2 (or more) randomized cohorts are compared. As noted in the previous DTaP and Hep B example, a control vaccine can itself be an existing licensed combination vaccine.

Serological end points are evaluated in a type of equivalence trial referred to as a noninferiority trial [36, 42]. The proportion of responders and/or geometric mean concentrations (GMCs) of antibodies can be analyzed in these trials [43]. Horne et al. [44] discuss the statistical aspects of noninferiority trials in this issue. The rationale for the use of serological end points is most apparent when a previously accepted correlation between such serological end points and clinical efficacy already exists [7, 34]. Even without a clear correlate of protection, comparisons of prespecified immune responses may also be used to evaluate new combination vaccines [7]. However, without an identified immune correlate of protection, or in cases in which the correlate is not well defined quantitatively, a decreased immune response for the new combination vaccine could be difficult to interpret (and may present problems for regulatory decisions). In such situations, it may not be possible to conclude that the new and old products are clinically comparable in regulatory decision making.

Serological end points are often important in the clinical development of a specific type of combination vaccine: multivalent products for a single etiological agent containing more than 1 antigen—for example, a 4-valent meningococcal vaccine. For such multivalent products, determining clinical efficacy for each distinct serotype in clinical trials may not be feasible because of problems, such as low incidence of disease caused by certain serotypes. Thus, for a single etiologic agent for which an immunological correlate of protection has been determined for 1 (or more) of the serotypes (or serogroups), serological end points may provide the basis for including other serotypes in the formulation [7, 45].

EFFICACY

This section will only cover a few topics pertaining to clinical end point efficacy trials. We refer the reader to regulatory doc-
CONCLUSION

Sponsors should devise a detailed development program that will allow the appropriate manufacturing, product, and clinical data to be obtained in an optimal sequence to support licensure of a new combination vaccine. This practice can help to minimize the total development time. Appropriate planning includes anticipating the needs of future clinical trials and activities necessary to complete vaccine development—for example, validation of critical assays, and manufacturing scale-up. The FDA offers specific regulatory guidance through meetings (by issuing formal meeting summaries) and other communications with FDA staff, as well as by providing documents relevant to the manufacture, product quality, and clinical testing of vaccines. Sponsors are encouraged to use these resources at appropriate times during vaccine development.

Acknowledgments

We thank Drs. A. Dale Horne, Mary Foulkes, and Donna K. Chandler, for their critical review of the article in manuscript.

References

27. International Conference on Harmonisation. Draft guideline on quality


