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Review

Regulatory considerations in the clinical development of vaccines indicated for use during pregnancy

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ABSTRACT

Despite supportive public health policies (e.g., ACIP recommendations), the potential for providing clinical benefit through maternal immunization has yet to be fully realized. For vaccines already licensed and approved for use in adults, specific FDA approval for use during pregnancy to prevent disease in the mother and/or infant may have a significant impact on uptake and usage in pregnant women. In addition, for either a licensed vaccine or a novel vaccine, FDA approval for use during pregnancy would result in labeling that would serve as a resource for practitioners and would facilitate the safe and effective use of the vaccine during pregnancy.

In the U.S., while many vaccines are approved for use in adults and most are not contraindicated for use in pregnant women, no vaccine is licensed for use specifically during pregnancy. Among the perceived obstacles hindering the clinical development of vaccines for use in pregnancy, regulatory issues are frequently cited. One aim of this article is to address the perceived regulatory obstacles. General concepts and regulatory considerations for clinical safety and effectiveness evaluations for vaccines indicated for use during pregnancy will be discussed. This discussion is not intended to establish data requirements or to articulate agency policy or guidance regarding *specific* vaccine products.

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1. Introduction

Vaccination of pregnant women provides important benefits to both mother and infant. For example, maternal immunization[1] with tetanus toxoid vaccines during the 3rd trimester of pregnancy has been successful in preventing neonatal tetanus in developing countries [2]. In addition, maternal immunization strategies may offer a new approach to preventing newborn and infant infectious disease due to pathogens such as group B streptococcus (GBS), respiratory syncytial virus (RSV), *Bordetella pertussis*, and *Streptococcus pneumoniae*, which are either not preventable by current vaccination strategies or for which protection prior to completion of the currently recommended primary vaccination series might be desirable [3–7]. Another possible benefit is the prevention of infectious disease in the mother, especially in instances where infection during pregnancy is associated with increased severity of disease and/or higher risk of complications resulting from illness, such as influenza [8,9].

The medical literature describes the use of a number of vaccines (primarily influenza, pneumococcal, and Tdap vaccines) during pregnancy. Data generated to date suggest that vaccines could be an effective approach to preventing disease in both the mother and the infant [10]. To our knowledge, the relevant publications have not identified safety concerns with regard to pregnancy or perinatal outcomes. However, from a regulatory perspective, these studies have limitations in their capacity to assess efficacy or safety. With some exceptions, they are not designed to demonstrate effectiveness using a clinical endpoint, such as protection from disease. The subset of studies that are randomized and controlled have limited statistical power to evaluate safety endpoints. Furthermore, the available data are not adequate to support definitive assessments of the potential for placentally transferred antibodies to diminish the effectiveness of infant vaccinations by interfering with the infant's immune response.

For certain vaccines licensed in the U.S., programmatic recommendations include guidance regarding use in pregnant women. For example, the Advisory Committee for Immunization Practices (ACIP) recommends administering influenza vaccine to pregnant women at risk for serious consequences from

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[1] "Maternal immunization" is frequently used to refer to vaccination prior to, during, or after pregnancy [1]. For the purposes of this article, "maternal immunization" refers to vaccination *during* pregnancy.

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influenza [11]. Recently, ACIP revised its recommendations on tetanus/diphtheria/pertussis (Tdap) vaccines to include their use during each pregnancy, irrespective of the patient's prior history of receiving Tdap [12]. Even though the influenza vaccines and Tdap vaccine are recommend by the ACIP for use in pregnancy, they are not licensed by regulatory agencies for use in pregnant women. From a U.S. FDA regulatory perspective, pre-licensure maternal immunization studies to evaluate the effectiveness of a vaccine used in pregnancy are needed in order for the prescribing information to include an indication and usage statement that specifically addresses use in pregnancy. However, lack of pre-licensure studies in pregnant women, i.e., lack of a specific "indication and usage" statement about use of the product in pregnant women in the product labeling, does not preclude use of these vaccines during pregnancy. Furthermore, neither class of licensed vaccine (Tdap and inactivated influenza vaccines) is contraindicated for use during pregnancy. Such use is not considered to be "off-label"; thus, programmatic recommendations (such as those from WHO, ACIP, and other national immunization technical advisory groups (NITAGs)) for use during pregnancy are not inconsistent with FDA labeling.

2. Applicable federal regulations

In the U.S., a single set of basic regulatory approval criteria apply to vaccines, regardless of the technology used in manufacture, the intended target population and the disease to be prevented. These regulations are contained in Title 21 of the Code of Federal Regulations (21 CFR) [13].

To obtain licensure to market a vaccine, including vaccines for maternal immunization, an applicant must show that the product is safe, pure and potent and that it can be manufactured in a consistent manner. Title 21 of the CFR, part 600, provides definitions for safety, purity and potency. For example, *safety* is defined as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered. . .taking into consideration. . .the condition of the recipient at the time". . . . (21 CFR 600.3(p)). Applying these criteria will necessitate a careful consideration of the character of the product, the methods of manufacture and the indication and use proposed for the vaccine. It follows that safety is relative, rather than absolute, and that safety will be evaluated in the context of a careful assessment of the risks and benefits of the vaccine. A successful product development program (see Section 3) culminates in an application for licensure of the vaccine product for the proposed indication, known as a BIOLOGICS LICENSE APPLICATION (BLA), and FDA approval of the application.

One critical element of the Agency's review of a BLA is the evaluation of the product's package insert (herein referred to as "labeling"). The content and format requirements for labeling information are prescribed by law and described in Title 21 CFR 201.56 and 201.57. A comprehensive discussion of the format, content, and functions of the labeling is beyond the scope of this article; please refer to the relevant regulations and FDA guidance documents for details.

With regard to the pregnancy subsection of the labeling, FDA recently revised the regulations characterizing what is known about use of the drug or biologic as it relates to pregnancy and reproduction. Among other things, the pregnancy and lactation labeling rule (PLLR) eliminates the letter categories (A, B, C, D, and X) designed to signify risk, and it provides a new framework to describe more clearly the available data on the potential risks associated with use of drugs and biologics during pregnancy and lactation [14,15].

Adoption of the principles articulated in the PLLR, as they apply to vaccine product labeling, will require discussion with the sponsors of both currently licensed vaccines and those in development. However, regardless of these changes, the pregnancy subsection of the labeling is unlikely to be directly relevant in the context of development of a vaccine specifically intended for use *during* pregnancy, for the reasons discussed in the following paragraph.

The clinical data available for vaccine labeling with regard to use during pregnancy typically come either from post hoc analyses of inadvertent exposures during pre-licensure trials designed to exclude pregnant subjects, or from uncontrolled, observational postlicensure studies (see discussion of pregnancy registries under Section 4.3). These data are summarized in Section 8 of the labeling, "USE IN SPECIFIC POPULATIONS". In contrast, the data necessary to support a license application for pregnancy-specific use of the vaccine will need to be generated in adequate and well-controlled studies with pre-specified endpoints designed to establish safety and efficacy in the pregnant mother and the infant. A detailed discussion of the study(ies), along with a summary of the data demonstrating the safety and effectiveness, would then be included in Sections 6, "ADVERSE REACTIONS" and 14, "CLINICAL STUDIES" of the labeling, respectively, in support of the indication for use described in Section 1, "INDICATIONS AND USAGE" [16].

The approach to clinical development of a vaccine for maternal immunization will depend on multiple variables, such as the epidemiology and natural history of the targeted disease, the characteristics of the product, and the proposed indication for use (e.g., protection of the mother, infant, or both). Early and frequent interactions between CBER and the sponsor are recommended for discussion and concurrence on the overall product development process and licensure pathway. During vaccine clinical development, meetings with sponsors serve as forums during which CBER can provide guidance regarding product characterization and nonclinical and clinical evaluation, and the sponsor can further outline the details of their chosen development pathway. Types of meetings that a sponsor can request are described in 21 CFR 312.47.

3. Stages of product development

Clinical development of a vaccine candidate is a continuous process which begins at the INVESTIGATIONAL NEW DRUG application IND (or pre-IND) stage, continues through the stages of the clinical investigation, and culminates in approval of a license application [17]. Before initiating a clinical investigation in the U.S., a sponsor submits an IND to CBER. The requirements for the IND content and format are described in the U.S. Code of Federal Regulations, 21 CFR 312.23. Briefly, the information submitted to the IND should include the scientific rationale for the investigational vaccine, the general investigational plan, pre-clinical animal safety data, a description of the composition, source, and the method of manufacture and control tests for the product and placebo (if applicable), final product release and stability testing data, the proposed Phase 1 clinical protocol, names and qualifications of the clinical investigator(s), and an Investigator's Brochure. In the case of vaccines already licensed for use in the U.S. (e.g., Tdap and influenza vaccines) pre-existing data for the product (such as reproductive toxicity studies, a licensed manufacturing process, and product quality control tests as well as safety and efficacy data in non-pregnant individuals), will support initiation of study(ies) in an advanced phase of clinical development (i.e., beyond phase 1).

The nonclinical and clinical development programs for a vaccine are both critical to the development program; usually these efforts should complement each other. The primary focus of this article is on clinical development; however, it should be emphasized that other critical aspects of establishing product safety include a thorough nonclinical evaluation of the product, establishment of well-controlled manufacturing processes, product characterization, development and validation of lot release tests and a stability