

**FDA Briefing Document**  
**Vaccines and Related Biological Products Advisory Committee Meeting**

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**Clinical Development and Requirements for Licensure of  
Vaccines Intended for Use During Pregnancy to Prevent  
Disease in the Infant**

## Table of Contents

|   |    |
|---|----|
| 1.0 Introduction .....  | 3  |
| 2.0 Basic licensure requirements and considerations regarding product labeling .....  | 4  |
| 3.0 Clinical development of vaccines for use during pregnancy to prevent disease in the infant .....  | 5  |
| 3.1 Safety evaluation.....  | 5  |
| 3.2 Overall size of the safety database .....   | 6  |
| 3.3 Efficacy studies.....   | 7  |
| 3.4 Establishing effectiveness when a clinical endpoint study is infeasible .....   | 8  |
| 3.5 Immunogenicity evaluations.....   | 8  |
| 4.0 Special considerations in the clinical development of <i>licensed vaccines</i> for use during pregnancy to prevent disease in the infant..... | 9  |
| 5.0 Studies conducted outside the U.S. ....   | 10 |
| 6.0 Summary .....   | 11 |
| 7.0 Committee discussion .....  | 11 |

## 1.0 Introduction

Maternal immunization<sup>1</sup> has long been pursued as a means to protect infants from vaccine-preventable diseases, as evidenced by maternal immunization programs to prevent neonatal tetanus (Miller, 1972). Scientific advances and increasing recognition of unmet potential have led to a recent surge in activity and interest in maternal immunization. For example, a number of vaccine developers are pursuing vaccine clinical development programs based on maternal immunization to support licensure for new vaccines to protect the infant. These include vaccines to prevent disease caused by respiratory syncytial virus (RSV) and group B streptococcus (GBS). In addition, a variety of stakeholders are increasingly engaged in studying and refining implementation programs for licensed vaccines recommended for use during pregnancy, such as inactivated influenza vaccines (IIV) and tetanus, diphtheria, and acellular pertussis (Tdap) vaccines.

Despite supportive public health policies (e.g., the Advisory Committee on Immunization Practices (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 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 to prevent disease in the infant would result in product labeling that would serve as a resource for practitioners and help ensure the safe and effective use of the vaccine during pregnancy.

From a U.S. FDA perspective, clinical studies to evaluating the safety and effectiveness of a vaccine used during pregnancy to protect the infant are needed in order for the prescribing information to include an indication and usage statement that specifically describes such use (Roberts & Gruber, 2015). For biological products, including vaccines, all indications must be supported by substantial evidence of effectiveness. CBER generally expects that such evidence is based on adequate and well-controlled studies.

In conceptualizing the program of clinical development of an investigational vaccine for use during pregnancy, a number of complex issues arise. For example, for some products being developed to protect against infectious diseases in the newborn, clinical endpoint efficacy trials may not be feasible in the U.S. because of low disease incidence. In addition, with regard to licensed vaccines that are recommended for use in pregnancy, conducting placebo- or active-controlled (i.e., unrelated vaccine control) trials in pregnant women may be considered unethical or present logistical challenges. For vaccines for which there is no scientifically well-established immune marker that

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<sup>1</sup> “Maternal immunization” frequently refers to vaccination prior to, during, or after pregnancy (Gall & Poland, 2011). For the purposes of this briefing document, “maternal immunization” refers to vaccination *during* pregnancy.

predicts protection and for which clinical endpoint efficacy trials may be unethical and/or infeasible, alternative methods to establish effectiveness will be needed. Other considerations include unique aspects of safety monitoring in pregnant women and infants and the potential for maternal immunization to interfere with immune responses to vaccines administered during infancy.

No specific vaccines and no product specific data will be presented and/or discussed at the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) meeting. However, in light of the above challenges, the committee will be asked to opine on the appropriate clinical study designs to support the safety and effectiveness of investigational vaccines, as well as study designs of licensed vaccines that are recommended for use in pregnancy to protect the infant. For example, on the issue of demonstrating effectiveness, the committee will be asked to discuss considerations regarding the potential use of immune marker(s) in lieu of clinical endpoint efficacy trials. Regarding safety the committee will be asked to discuss safety endpoints to be evaluated in both the mother and the infant, as well as the duration of follow-up for infants born to mothers immunized during pregnancy. In addition, the committee will be asked to discuss approaches to evaluating interference with immune responses to vaccination among infants born to mothers immunized during pregnancy.

## **2.0 Basic licensure requirements and considerations regarding product labeling**

In the U.S., Title 21 of the Code of Federal Regulations (21 CFR) includes regulations applicable to the development and licensure of vaccines. The basic regulatory requirements for licensure, a demonstration of safety (21 CFR 600.3(p)), purity (21 CFR 600.3 (r) and potency (21 CFR 600.3(s)), apply regardless of the technology used in manufacture, the intended target population and the disease to be prevented. With regard to potency, FDA interprets potency to include effectiveness.

Furthermore, labeling regulations (21 CFR 201.56 and 201.57) require that prescribing information must not be false or misleading and must not contain implied claims or suggestions of uses for which there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. The “Indications and Usage” section of labeling should clearly convey the use(s) for which the product has been shown safe and effective, accurately reflecting the scientific evidence. For biological products including vaccines, all indications listed in the “Indications and Usage” section must be supported by substantial evidence of effectiveness. Such evidence is expected to be derived from adequate and well-controlled studies. Approaches to accruing data adequate to support a pregnancy-specific indication for prevention of infant disease are discussed below.

As part of a broader effort to further improve the content and format of prescription drug labeling, FDA recently published a final rule, the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and*

*Lactation Labeling*, referred to as the “Pregnancy and Lactation Labeling Rule” (PLLR). Among other things, the 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 regarding potential risks associated with use of drugs and biologics during pregnancy and lactation (“Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Pregnancy and Lactation Labeling,” 2014; Marshall & Gruber, 2012). PLLR requires an evaluation of available information about a product’s use in pregnancy and provides an opportunity to update labeling when new information about use of the vaccine in pregnancy becomes available.

Although it changes the organization of the pregnancy section of the label, the PLLR does not change the primary focus, which is to characterize the safety data that are available regarding use in pregnancy. The PLLR does not sanction the inclusion of data that imply efficacy for a claim that is not established as an indication. The reason for this is related to one of the overarching principles of product labeling, which involves indication(s) for use: “Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section [the Indications and Usage section] (21 CFR 201.57(c)(2)(iv).” As a result, the PLLR is not anticipated to have an impact on the requirements for substantial evidence of effectiveness to support vaccine indications.

### **3.0 Clinical development of vaccines for use during pregnancy to prevent disease in the infant**

#### **3.1 Safety evaluation**

The potential risks associated with immunizing pregnant women need careful evaluation. Theoretical adverse effects include those caused by 1) constituents of the vaccine product (e.g., adjuvants and excipients), 2) inherent biological activity of the antigens, and 3) the immune response induced by the vaccine. An additional theoretical concern is that the vaccine-associated inflammatory reaction necessary to generate an immune response in the mother could disturb maternal mechanisms that maintain tolerance of foreign fetal antigens, potentially leading to adverse pregnancy outcomes, such as spontaneous abortion (SAb) or intrauterine growth restriction (IUGR), or preterm birth (PTB) (Kallikourdis & Betz, 2007; Raghupathy, 1997; Williams, 2012).

The theoretical risks discussed above apply to all vaccine candidates, including inactivated, subunit, and toxoid-conjugated products. Live-attenuated vaccines and viral or bacterial vectors invoke additional pregnancy-related safety concerns in some cases.

Evaluation of safety for a product that will be specifically approved for use in pregnant women presents (at least) two unique and challenging issues that will require special

consideration and potentially some adjustments compared with typical vaccine safety assessment.

1. Regardless of the candidate vaccine's intended benefit (for the mother, the infant, or both), the vaccine may pose risks for both mother and infant. Thus, at each stage of clinical development, safety must be considered in both the mother and infant.
2. Complications of pregnancy (i.e., adverse outcomes) are not uncommon, even among pregnancies identified as "low risk" (Evers et al., 2010).

Pregnancy is a dynamic state that carries certain risks. In vaccine trials in pregnant women, a higher frequency of adverse events commonly observed in men and non-pregnant women, as well as additional types of adverse events are expected. This is expected across the spectrum of severity of adverse events. Less serious events (e.g., joint pain, carpal tunnel syndrome, gastroesophageal reflux, and constipation) as well as more serious events (e.g., severe hypertension and deep vein thrombosis) are likely to occur more frequently in pregnant women. Onset of symptoms will inevitably occur in temporal association with vaccination in some women (Siegrist, Lewis, Eskola, Evans, & Black, 2007).

Thus, before conducting studies in pregnant women, it will be essential to establish a systematic approach to classifying adverse events to facilitate assessment when an adverse event is observed in the clinical trial. The sponsor should develop a framework for defining adverse events (AE) as maternal or infant (e.g., intrauterine growth restriction (IUGR) is a complication of pregnancy (*maternal*), whereas small for gestational age (SGA) is an *infant* AE). A recent series of papers published by an NIH-organized consortium of subject matter experts is a useful resource (Beigi, Goldkind, & Jevaji, 2013; Munoz et al., 2013; Sheffield et al., 2013). Ultimately, the sponsor must be able to demonstrate that it is safe to administer the vaccine during pregnancy for both the mother and infant, and that the benefit-risk balance is favorable.

Another critical consideration in the design of maternal immunization studies is the approach to safety surveillance and the duration of safety follow-up for the infant. The appropriate duration of follow-up will depend on many factors, such as the properties of the investigational product (e.g., inclusion of an adjuvant) and the population being studied. Safety parameters utilized in infant vaccine studies can form the basis of the approach to evaluation of safety in infants in maternal immunization studies. However, additional consideration should be given to including growth and development outcomes.

### **3.2 Overall size of the safety database**

A clinical program for establishing safety is directed in part toward assessing the vaccine's "reactogenicity". Reactogenicity refers to a subset of adverse events that describes and is characterized by the inflammatory response to vaccination, both local

(e.g., injection site pain, tenderness, erythema) and systemic (e.g., fever, headache, myalgia)("Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials," 2013). Through solicitation for a set of adverse events and assessment using toxicity grading scales in a well-controlled, blinded, randomized study, adequate evaluation of reactogenicity typically can be achieved with a database in the low hundreds of subjects.

With regard to relatively more common adverse outcomes that are specific to pregnancy, sponsors should monitor and record these events, analyze the rates in the vaccine versus control groups, and in some cases compare to background rates estimated from a comparable population. For example, first trimester spontaneous abortion and preterm birth are fairly common pregnancy outcomes, but an imbalance of such events in a randomized, blinded, controlled trial might suggest a safety concern. Therefore, the criteria used to calculate sample size (both for individual studies and for the purpose of proposing the size of the overall safety database in the pre-licensure development program) should take into account the capacity to characterize the relative risk of common adverse pregnancy outcomes.

CBER recognizes that the ability to detect a small magnitude of increased relative risk of rare unanticipated adverse outcomes is limited, even with a relatively large sample size. Thus, unless available data suggest a specific risk (e.g., from earlier studies in pregnant women), clinical studies to detect a slight increase in the relative risk of uncommon adverse events (e.g., neurocognitive adverse outcomes or individual congenital anomalies) are not anticipated to be necessary pre-licensure. Sponsors are expected to consider the overall benefit-risk assessment when they propose the size of the overall safety database. Typically, the most appropriate time to discuss and establish the projected size of the safety database is during End of Phase 2 meetings with CBER.

### **3.3 Efficacy studies**

The gold-standard for demonstrating effectiveness of a vaccine is a prospective, randomized, blinded, well-controlled study, wherein the control arm receives placebo (or active control, i.e. an unrelated vaccine) and the primary endpoint is prevention of clinical disease. The Agency's expectation is, where feasible, that data generated in a study(ies) using this approach will be necessary to support a license application for a pregnancy-specific indication either for a novel vaccine or for a new indication for an existing vaccine. If the manufacturer prefers to take a different approach, the first step is to provide compelling evidence that such a prospective, randomized, well-controlled study design is infeasible and/or unethical. Having established and agreed upon that concept with CBER, the next step is to propose an alternative; some potential alternatives are discussed below.

CBER anticipates that most new pregnancy-specific indications will focus on prevention of disease in the infant (e.g., "[VACCINE NAME] is indicated for use during pregnancy for the prevention of [DISEASE NAME] in the infant from birth to 6 months of age."). For

this scenario, although safety must be established in both mother and infant, CBER's current thinking is that the requirement for demonstration of effectiveness will apply solely to the infant.

### **3.4 Establishing effectiveness when a clinical endpoint study is infeasible**

If a sponsor determines and establishes that a randomized, blinded, well-controlled clinical endpoint efficacy trial is infeasible and/or unethical, they should develop a proposal to demonstrate effectiveness through an alternative approach. In most cases, this will be based on the use of a relevant immune marker. However, other clinical endpoints can be considered. A potential example comes from the clinical development of vaccines intended to prevent congenital cytomegalovirus (cCMV) disease. Pre-licensure studies designed to demonstrate prevention of cCMV disease are unlikely to be feasible because of the sample size and the length of follow-up needed to detect hearing loss (the most common cCMV manifestation) and other later sequelae in the infant. Therefore, it may be reasonable to use a primary endpoint of prevention of cCMV *infection* (determined by laboratory assay, such as PCR or virus isolation from urine or saliva samples from the newborn) to infer effectiveness in the prevention of cCMV *disease* (Krause et al., 2013).

In support of their proposal for demonstration of effectiveness, the sponsor should provide data-driven rationale for why an alternative endpoint can be used to infer effectiveness. If the scientific evidence is supportive and agreement is reached with CBER on this in advance, success on pre-specified immunologic (or other) endpoint(s) may be sufficient to support effectiveness for regulatory approval of a specific indication.

To the degree that uncertainty exists regarding the capacity of an alternative endpoint to predict effectiveness, use of such an endpoint may not support traditional approval. In such cases, if the endpoint is determined to be "reasonably likely to predict clinical benefit", it may be considered as adequate for an accelerated approval. A detailed discussion of licensure pathways (e.g., accelerated approval, the "animal rule", etc) is beyond the scope of this briefing document and VRBPAC discussion. What is important to note here is that licensure under the accelerated approval regulations confers on the sponsor the requirement to conduct study(ies) post-licensure to verify and describe clinical benefit.

### **3.5 Immunogenicity evaluations**

During clinical development, the immunogenicity of a vaccine should be evaluated in the mother, and passive transfer of maternal antibody should be assessed in the infant. Assessments may include efficiency of placental antibody transport, persistence of maternal antibody in the infant, and investigation of functional antibodies. These data may form the basis for using immune parameters to bridge effectiveness from immunogenicity endpoints (i.e., "bridging studies"; see below). Validation of assays to evaluate immune parameters is essential.

For certain vaccines, immunization of pregnant women results in the passive transfer of antibodies that may interfere with the ability of the offspring to mount an optimal immune response to either the same or other vaccine antigen(s)(Bell et al., 2007), some of which may be included among routinely recommended infant and childhood vaccines. It will be necessary to evaluate post-vaccination immune responses to routinely recommended childhood vaccines among control infants compared to infants born to mothers who have been immunized during pregnancy.

Particularly in the case of Tdap vaccines, some evidence suggests that the immune response to primary vaccination may be diminished among infants whose mothers were vaccinated. For example, in a randomized, placebo-controlled study of one Tdap vaccine in pregnant women, the infants of the vaccinated mothers had substantially diminished antibody responses to both the diphtheria toxoid and to all the pertussis antigens at 7 months of age (after the 2, 4, and 6 month doses of DTaP vaccination)(Munoz et al., 2014). Further clinical studies are necessary to assess the potential impact of this phenomenon on effectiveness, particularly with regard to the prevention of pertussis, in order to support an overall benefit-risk assessment. In other words, both the benefit of higher anti-pertussis antibodies in the first 2-4 months of life and the potential risk of diminished anti-pertussis responses to primary vaccination during the remainder of the first year of life are incompletely characterized.

#### **4.0 Special considerations in the clinical development of *licensed vaccines for use during pregnancy to prevent disease in the infant***

For certain vaccines licensed in the U.S., programmatic recommendations for use in pregnant women have been endorsed. For example, the ACIP has advised that “routine influenza vaccination is recommended for all women who are or will be pregnant (in any trimester) during influenza season.” (“Prevention and control of seasonal influenza with vaccines,” 2013). In 2012, ACIP revised its recommendations on Tdap vaccines to include a recommendation for their use during each pregnancy, irrespective of the pregnant woman’s prior history of receiving Tdap (“Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012,” 2013).

The general approach taken by the ACIP is that the benefit of vaccination among pregnant women usually outweighs the risk for potential adverse effects in the mother or developing offspring when (a) the risk for disease exposure is high, (b) infection poses a special risk to mother and fetus, and (c) the vaccine is unlikely to cause harm. Of note, lack of a specific “indication and usage” statement about use of the product in pregnant women to prevent disease in the infant in the FDA approved product labeling does not preclude use of these vaccines during pregnancy. Furthermore, neither class of licensed vaccine (Tdap and IIV) 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.

As described above (Section 3.3 Efficacy studies), CBER maintains that the gold standard for establishing effectiveness should be a prospective, randomized, blinded, well-controlled study, wherein the control arm receives placebo (or active control, i.e. an unrelated vaccine) and the primary endpoint is prevention of clinical disease in the infant. However, given current ACIP recommendations for the use of IIV and Tdap vaccines during every pregnancy, CBER recognizes that the design and implementation of such studies of licensed vaccines during pregnancy presents considerable challenges.

Given these challenges, the appropriate approach to establishing effectiveness depends on the specific product and the specific situation. For example, in the case of IIV, several randomized, blinded, well-controlled studies have been conducted (and several are ongoing) which are designed to assess influenza disease outcomes in infants born to mothers vaccinated with IIV during the pregnancy (Madhi, Nunes, & Cutland, 2014; Zaman et al., 2008). This suggests that comparable studies could be conducted by the vaccine manufacturers. In addition, precedent exists for manufacturers to use clinical data generated by a 3<sup>rd</sup> party to support an efficacy supplement to their BLA to include the clinical data in the package insert (Monto et al., 2009). CBER is prepared to discuss the use of such pre-existing data with a particular product to support a licensure application seeking an additional indication for prevention of disease in the infant after vaccination of the pregnant mother.

Given the challenges involved in the study of licensed vaccines already recommended for use during pregnancy, alternate approaches to demonstrating vaccine effectiveness, including observational studies may be considered. Such studies would, at a minimum, need to be prospectively designed; and would need to incorporate approaches to limit bias.

## **5.0 Studies conducted outside the U.S.**

Sponsors planning to conduct maternal immunization studies should submit an IND to FDA. FDA regulations permit the acceptance of foreign clinical studies in support of a BLA approval, provided certain conditions are met. Foreign studies performed under an IND must meet the requirements of 21 CFR Part 312.120. Specifically, under 21 CFR 312.120, FDA can accept as support for an IND or to support an application for marketing approval, a well-designed and well-conducted foreign clinical study not conducted under an IND, if certain conditions are met, including that the study was conducted in accordance with GCP and including review and approval by an independent ethics committee.

In a situation where a clinical endpoint efficacy trial for a vaccine proposed for maternal immunization is infeasible because the infant disease has a low incidence in the U.S., it may be possible to conduct the clinical efficacy trial(s) in a region or country with higher incidence of the disease of interest. In these circumstances, a clinical bridging study may be necessary to provide scientific support that the vaccine will be effective in preventing disease in infants when administered to pregnant women in the U.S.

When planning to perform an efficacy study outside the U.S., background epidemiological data should be obtained in the intended efficacy trial population to support the rationale for selecting that specific population and to estimate the number of participants needed for a successful clinical trial. Consideration should be given to potential differences in efficacy and immunogenicity between populations due to differences in genetics, nutritional status, background infections, and standard of care. Some of these principles are discussed in the ICH E5 guideline. Because of these potential differences in clinical trial settings, sponsors are advised to consider obtaining preliminary safety and immunogenicity data using the candidate vaccine in the specific target population prior to conducting the phase 3 efficacy study(ies).

## **6.0 Summary**

The regulatory approval process for vaccines indicated for maternal immunization to prevent disease in the infant will be guided by regulations outlined in Title 21 of the Code of Federal Regulations (21 CFR) and standards set forth in applicable guidance documents, such as the ICH guidelines and FDA Guidance documents. The development program and licensure path will be product-specific and should be designed to support the indication being sought.

## **7.0 Committee discussion**

The committee will be asked to discuss considerations regarding the data necessary to support the safety and effectiveness of both investigational and licensed vaccines being developed for use in pregnancy to prevent disease in the infant.

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