Guidance for Industry

Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY:[1]

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I. INTRODUCTION

The purpose of this document is to provide sponsors with guidance for the conduct of reproductive toxicity studies for preventive vaccines and to consider establishing clinical pregnancy registries for preventive vaccines indicated for females of childbearing potential and pregnant individuals[2]. The recommendations set forth in this document pertain to the assessment of the reproductive toxicity potential of preventive vaccines for infectious diseases.

The Center for Biologics Evaluation and Research (CBER) reviews a broad spectrum of investigational vaccines for the prevention of infectious diseases indicated for immunization of adolescents and adults. Thus, the target population for vaccines often includes females in their reproductive years who may become pregnant during the time frame of vaccination. In addition, there are a number of vaccines in clinical development specifically intended for maternal immunization with the goal of preventing infectious disease in the vaccinee and/or young infant through passive antibody transfer from mother to fetus. There are special considerations in assessing the risks versus the benefits of immunization programs for pregnant women and/or females of childbearing potential that should be addressed during the pre-marketing phase of the product. In addition to potential adverse effects on the safety of the pregnant women, there may be concerns that the vaccine exerts adverse effects on normal fetal development and/or the development of an active immune response in infants born to mothers vaccinated during pregnancy.

In the past, during the pre-marketing phase there were no data collected regarding the vaccine's safety in pregnant women. In general, during clinical development of vaccines not intended for use during pregnancy, pregnant women are actively excluded from participation in clinical trials. In addition, if pregnancy occurs during a study, treatment is usually discontinued and the woman is dropped from the trial.

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[1] This guidance has been prepared by the Maternal Immunization Working Group in the Center for Biologics Evaluation and Research at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the assessment of the reproductive toxicity potential of preventive vaccines for infectious diseases. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] This document does not address concerns regarding male reproductive toxicity and fertility studies.

However, as more females of child-bearing potential participate in clinical trials of investigational products and more preventive vaccines are being developed that are indicated for adolescents and adults, there is increasing concern for the unintentional exposure of an embryo/fetus before information is available regarding the potential risk versus benefit of the vaccine. In addition, following approval, vaccines may be recommended for use in pregnant women or there may be situations of inadvertent exposure of the pregnant woman and her fetus to the vaccine. In these situations, in the absence of clinical data it is difficult for the practitioner to make an informed risk assessment. Therefore, pre-clinical reproductive toxicity studies provide an important systematic approach and may frequently present the only data source upon which to base estimations of risk to the pregnant mother and/or the developing fetus. However, there is virtually no scientific literature on animal reproductive toxicity testing for vaccine products. This guidance is intended to outline general and specific considerations that should be taken into account in the assessment of reproductive toxicity for preventive vaccines.

II. DEFINITIONS

A. Vaccine

For the purpose of this document a vaccine is a product, the administration of which is intended to elicit an immune response(s) that can prevent and/or lessen the severity of one or more infectious diseases. A vaccine may be a live attenuated preparation of bacteria, viruses or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombinant DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above (Ref. 1).

B. Reproductive Toxicology

Reproductive Toxicology is “the study of the occurrence, causes, manifestations, and sequelae of adverse effects of exogenous agents on reproduction” (Ref. 2).

C. Developmental Toxicity

Developmental toxicity is any adverse effect induced prior to attainment of adult life. This includes effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally (Ref. 3)

III. VACCINE TARGET POPULATION AND TIMING OF PRE-CLINICAL REPRODUCTIVE TOXICITY STUDIES

Reproductive toxicity studies should be conducted for vaccines indicated for adolescents and adults and for vaccines that are indicated or may have the potential to be indicated for immunization of pregnant women. However, there are currently differences in the timing of these studies to support inclusion of either target population in clinical trials.

Maternal immunization: Data from reproductive toxicity studies for products indicated specifically for immunization of pregnant women should be available prior to the initiation of any clinical trial enrolling pregnant women.

Females of childbearing potential: For vaccines indicated for females of childbearing potential, subjects may be included in clinical trials without reproductive toxicity studies, provided appropriate precautions are taken, such as pregnancy testing and use of birth control. For these products, data from reproductive toxicity studies should be included with the initial Biologics License Application submission, if they were not submitted earlier in the Investigational New Drug Application (IND).

The need for these data is supported by the following consideration: a) the target population for vaccines often includes women in their reproductive years who may become pregnant during the time frame of vaccination; b) clinicians are confronted with situations where immunization of pregnant women may be appropriate, e.g., when pregnant women are thought to be at higher risk from complications of a vaccine preventable disease (e.g. influenza); and c) vaccine labeling must have a statement about use during pregnancy (21 CFR 201.57 (f)(6)). For instance, without animal reproductive toxicology information, inactivated/recombinant vaccines would usually be pregnancy category C which does not assist the physician with regard to risk assessment in special clinical settings. Currently, males may be included in phase I, II, and III clinical trials in the absence of male fertility studies, although such studies may be recommended for certain products in the future.

IV. DESIGN OF REPRODUCTIVE TOXICITY STUDIES

A. General Considerations

Each vaccine should be evaluated on a case-by-case basis whereby the features of the product and its intended clinical use should be taken into account when determining the design of the reproductive toxicity study. Interpretation of the data derived from the reproductive toxicity study should include assessing whether any correlation exists between risks identified in animals with potential risks in humans.

1. Previous clinical experience

All available clinical experience in pregnant females should be considered for any potential application to the design of reproductive toxicity studies in animals. Clinical experience derived from immunization of pregnant women may be helpful in the evaluation of the potential for any adverse outcome on the viability and development of offspring. Such information may also aid in the design/monitoring of appropriate pre-clinical studies, and for product labeling.

However, clinical data that may have been obtained from a small number of pregnant women enrolled in non-IND studies, e.g., immunized with an investigational vaccine, will not replace the need for comprehensive animal reproductive toxicity studies.

2. Previous pre-clinical experience

All data generated from prior acute or repeat dose pre-clinical toxicity studies should be reviewed for their possible contribution to the interpretation of any adverse developmental effects that appear in the reproductive toxicology studies, i.e., fetal toxicity secondary to maternal toxicity.

3. Application of ICH guidance document S5A

CBER is recommending use of the ICH S5A guidance document entitled "Detection of Toxicity to Reproduction for Medicinal Products," as a point of reference to assist in the design of reproductive toxicity studies in order to assess the potential teratogenic effect of biological products in general (Ref. 3). However, while the ICH document provides initial guidance, it is important to note that the best way to design a reproductive toxicity study for a biological product is to allow for a flexible framework. Preventive vaccines present a diverse class of biological products including live attenuated, inactivated, recombinant, polynucleotide, polysaccharide, and protein antigens, vectored vaccines, conjugate vaccines, adjuvanted vaccines or they may consist of a combination of different vaccine antigens. Thus, it is evident that product specific issues frequently arise that may require the pre-clinical testing to be tailored to the vaccine product under consideration. Thus, the sponsor should establish an early dialogue with CBER to reach agreement on specific design issues and study endpoints prior to the conduct of the study.

B. Specific Considerations

1. Immunological parameters

The most important feature distinguishing a vaccine from drugs and other biological products is the immune response that the vaccine is intended to induce. Thus, in addition to evaluating the potential for adverse effects on the mother and the developing fetus caused by the inherent properties of the vaccine antigen and/or vaccine formulation; reproductive toxicity studies should be designed to also assess the vaccine induced immune response as well as the potential for vaccine induced immunopathologic effects (i.e., the development of antibodies cross-reacting with fetal tissues and auto-antibodies or other responses that may adversely affect the development of the fetus). The assessment should include a) the detection of antibody production in the pregnant animal, b) the antibody transfer from the pregnant female to the fetus through antibody measurements in the newborn, and c) the presence, persistence and effects of the antibody response in the newborn. Serum samples collected from pregnant animals, cord blood or fetal tissues as well as blood samples from newborn animals should be assessed for antibody specificity and kinetics. Such evaluation may also include an examination of fetal tissue for potential cross-reactivity with passively transferred antibodies induced by immunizing the pregnant animal with the vaccine product.

2. Animal model

It is recognized that animal models are not always available and/or that responses induced in an animal model may not always be predictive of the exact human response. However, when designing a reproductive toxicity study, efforts should be made to establish a relevant animal model. Furthermore, the sponsor should provide a rationale for either the choice of the animal model or the lack thereof. The reproductive toxicity study does not necessarily need to be conducted in the traditional species, i.e., rats and rabbits. There is also no specific request for the routine use of two species, i.e., one rodent and one non-rodent at this time. Ideally, the vaccine should elicit an immune response in the animals. The immunogenicity of the vaccine may be evaluated in pre-clinical trials in non-pregnant animals. In cases where lack of an appropriate animal model hinders the assessment of an immune response, reproductive toxicity studies are still useful in providing important information regarding the safety of the vaccine components/formulation in the pregnant animal and/or the developing fetus.

3. Dose

Reproductive toxicity studies should include a dose response that brackets the intended clinical dose level in order to a) assess the potential toxic effect(s) that a particular dose may have on the dam and on the conceptus, b) define a safe dose, and c) define the

dose capable of eliciting an immune response. The dosing regimen should include a full human dose equivalent (e.g., 1 human dose = 1 rabbit dose). A dose scaled down because of feasibility considerations should ordinarily still exceed the intended human adult dose by at least 15 fold on a mg/kg basis.

4. Schedule

The immunization interval and frequency of immunization(s) in a reproductive toxicity study should be based on the clinically proposed immunization interval. Thus, episodic dosing of pregnant animals is likely to be more relevant than daily dosing. Also, modifications to the dosing frequency may be necessary depending on the kinetics of the antibody response induced in the animal. In certain cases it may be necessary to also administer a priming dose to the female prior to conception to allow for an immune response to occur considering the short gestation periods of the most commonly used animal models, i.e. rabbits and rats.

5. Exposure period

An important area to evaluate is the potential adverse effect(s) of the vaccine on embryo-fetal development. Thus, it is recommended that the vaccine be administered during the period of organogenesis, that is, the female is exposed to the vaccine from implantation to birth. In addition, to evaluate effects on the pregnant/lactating female and on early post-natal development of the offspring the study should also include a follow-up period from birth to weaning. These studies are defined as stages C-E in the ICH S5A document.

6. Follow-up period

Reproductive toxicity studies should include an in-life phase, i.e., follow-up of the pups from birth to weaning, to assess the immune response induced by the vaccine including the evaluation of a) maternal antibody transfer to the offspring, b) magnitude and persistence of antibodies in the newborn pups, c) effects of antibodies in the newborn, i.e., the potential interaction with host tissues, and d) presence of antibody in milk. In addition to an assessment of the immunologic parameters, the follow-up period would also allow an evaluation of neonate adaption to extra-uterine life, i.e., postnatal development and growth as well as maternal behavior. For certain vaccines, there may be concerns that immunization of pregnant females may interfere with the ability of the offspring to mount an active immune response to either the same or a related vaccine antigen. Such concerns may need to be addressed on a case-by case basis in clinical immunogenicity studies in infants born to mothers that have been immunized with the vaccine during pregnancy.

7. Endpoints

In addition to an evaluation of the immunological parameters, the assessments may include maternal weight gain, clinical observations, implantation number, corpora lutea number, litter size, live fetuses, fetal and embryonic deaths, resorptions, pup weight, crown-rump length as well as incidence of external, visceral and skeletal malformations. Postnatal evaluations may include maternal-newborn relationship, neonate adaptation to extra-uterine life, pre-weaning development and growth, survival incidence, developmental landmarks and functional testing (Ref. 3). The evaluation of a given endpoint will depend on the features of the product.

V. VACCINE PRODUCT CLASS

Reproductive toxicity studies should be performed in advance for every final clinical vaccine formulation used in studies that enroll pregnant women. To avoid performing multiple reproductive toxicology studies during development, sponsors may find it advantageous to conduct Phase 1 and Phase 2 studies in non-pregnant subjects. Results from these studies can be used as the basis for advancing the most promising product(s) to studies that enroll pregnant women. The decision to perform multiple reproductive toxicity studies for vaccine products falling into a similar or the same product class (e.g., 9- versus 11-valent pneumococcal conjugate vaccine; multivalent versus monovalent Group B *Streptococcus* (GBS) vaccine products) will need to be made on a case-by case basis.

VI. ESTABLISHMENT OF PREGNANCY REGISTRIES

If the vaccine is administered to females of childbearing potential or is specifically indicated for immunization during pregnancy, the safety of that vaccine in human pregnancy may need to be further evaluated in a systematic manner under a Phase IV commitment. Alternatively, data on potential risks with the use of the vaccine in pregnant individuals may be obtained for already marketed products in order for the sponsor to update the product label. It is therefore recommended that pregnancy registries are established for the purpose of monitoring the post-licensure experiences from vaccinated pregnant women and their offspring to determine risks associated with use of the vaccine during pregnancy. The decision to conduct a pregnancy registry should be made on a case by case basis and may depend on several parameters such as the availability and extent of data derived from pre-clinical and clinical studies. The agency has also published for comment, guidance with regard to the design of pregnancy registries and suggested outcomes entitled “Draft Guidance for Industry: Establishing Pregnancy Registries”(Ref. 4).

VII. REFERENCES

1. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (January 1999)

2. Ecobichon, Donald. "Reproductive Toxicology" in CRC Handbook of Toxicology, Derelanko M. and Hollinger M, Eds., CRC Press, 1995

3. International Conference on Harmonization (ICH) Harmonized Tripartite Guideline "Detection of Toxicity to Reproduction for Medicinal Products, (59 FR 48746, September 22, 1994)

4. Draft Guidance for Industry: Establishing Pregnancy Registries (June 1999)