MEMORANDUM

Date: September 17, 1998

From: Marion F. Gruber, Ph.D, DVRPA/OVRR

To: M.C. Hardegree, M.D., Director, OVRR
N. Baylor, Ph. D.

Through: K. Goldenthal, M.D., Director, DVRPA

Subject: POINT PAPER "PRECLINICAL REPRODUCTIVE TOXICITY STUDIES FOR VACCINES"

Purpose:

a) To obtain feedback and concurrence from OVRR and CBER upper management on the recommendations made by the maternal immunization working group with regard to reproductive toxicity study requirements for vaccines pending licensure and to obtain concurrence that these recommendations may be used in discussing reproductive toxicity study requirements with sponsors

b) To generate a working document to promote consistency among OVRR reviewers

This document does not contain detailed proposals for reproductive toxicity studies for specific vaccine products. These will be the subjects of further discussions by the maternal immunization working group provided that concurrence on the concepts contained in this document have been obtained.

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Rationale: Maternal immunization is intended to prevent infectious disease in the vaccinee and/or young infant through passive antibody transfer from mother to fetus. Although preclinical reproductive toxicity studies prior to licensure of vaccines intended for maternal immunization and/or women of child bearing age are critical in assessing the potential for the developmental toxicity of the product, OVRR has no written policy to date addressing such requirements. In addition, the performance and design of preclinical reproductive toxicity studies for vaccines to support their use for maternal immunization has not been addressed in the scientific literature. A maternal immunization working group was formed in January of 1998 which includes scientific staff from OVRR and toxicologists from OTRR and CDER[1].

The purpose of this working group is to optimize the advice given to sponsors regarding the preclinical testing for specific

[1]Previous attendees of the maternal immunization working group: *CBER/OVRR*: M.Gruber, M.Hardegree, N.Baylor, K.Goldenthal, D.Chandler, K.Midthun, D.Pratt, V.Johnson, J.Clifford, L.Ball, A.Geber, C.Frasch, C.Deal, L.McVittie, L.Henchal, L.Falk, M.Monser, P.Richman, B.Sheets; *CBER/OTRR*: D.Green, M.Serabian, CDER:K.Hastings

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vaccine products as well as to develop comprehensive policy for reproductive toxicity study requirements for vaccines indicated for maternal immunization and/or immunization of women of childbearing age.

The following summarizes the recommendations for reproductive toxicity studies for vaccines:

Preclinical Reproductive toxicity studies for vaccines indicated for immunization of pregnant women:

Reproductive toxicity studies should be conducted for every vaccine indicated for immunization of pregnant women. These studies should be completed prior to initiation of Phase 1 clinical trials involving pregnant women.

In addition to safety trials in pregnant women pre-licensure, pregnancy registries should be established for the purpose of effectively monitoring for any adverse events experienced by the vaccinated pregnant females, as well as to track any developmental toxicities displayed by the offspring post licensure.

Preclinical reproductive toxicity studies for vaccines indicated for immunization of adolescents and adults

Reproductive toxicity studies should be conducted prior to licensure for all vaccines indicated for adolescents and adults of childbearing age due to the increasing number of vaccines that are recommended for this population even though this has not been required by OVRR in the past. This position is further supported by the fact that reproductive toxicology studies are required for some products licensed by OTRR and for the majority of products that are regulated by CDER. Further discussions will be needed regarding the stage of product development by which the preclinical reproductive toxicity evaluation should be completed.

It is recommended that pregnancy registries be established to monitor the safety of these vaccines post licensure. Of particular concern is the administration of the vaccine to pregnant individuals.

[Note that in CDER data from teratogenicity studies are generally obtained before proceeding to Phase 2 studies. All reproductive toxicity studies, to include male fertility, teratogenicity, and postnatal development, are generally conducted before initiating Phase 3 clinical trials.]

Preclinical versus clinical experience with vaccines:

Clinical data that may have been obtained from a small number of pregnant women enrolled in non-IND studies immunized with an investigational vaccine do not replace the need for comprehensive reproductive toxicity studies.

However, 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 preclinical studies.

Design of reproductive toxicity studies

Males

The potential adverse effects on male fertility should be assessed if the vaccine indication includes the male population. This is particularly important for products that are given to military forces, e.g., the Anthrax and Botulinum toxoid vaccine. However, additional discussion will be required regarding the details of the types of studies needed for these products. The ICH S5B document may serve as guidance in the design of these studies (Reproductive Toxicology: Male fertility studies, April 5, 1996, FR 15360, Vol.61, No. 67)

Females

While the type of study performed depends on the clinical indication and the product, in general, relevant information can be obtained by conducting Segment II teratology studies and/or studies designed following stages C - E of the ICH guidance document entitled "Detection of Toxicity to Reproduction for Medicinal Products" (September 22, 1994, FR 48746, Vol.59, No. 183)

It is important that a postpartum follow-up period be included in the design of the study, in order to evaluate the active immune response in the offspring following vaccination of pregnant females.

The reproductive toxicity study should be designed to include:
1) the detection of antibody production in the pregnant animal;
2) the feasibility of antibody transfer from the pregnant female to the fetus through antibody measurements in the newborn.

General Considerations

All available clinical experiences in pregnant females should be considered for any potential application to the design of reproductive toxicity studies in animals.

All data generated from prior acute or repeat dose preclinical toxicity studies should be reviewed for their possible contribution to the interpretation of any adverse developmental effects that appear in the reproductive toxicology studies.

Reproductive toxicity studies should include a dose response component in order to assess 1) the ability of a certain dose of vaccine to elicit an antibody response and 2) the effect(s) that a particular dose has on the dam and on the conceptus.

The immunization interval and frequency of immunization(s) in a reproductive toxicity should be based on the clinically proposed immunization interval and its timing, i.e., use of the vaccine at pre-conception or during the 1st, 2nd, and/or 3rd trimester.

Reproductive toxicity studies for vaccines similar in structure and/or activity to other compounds:

Although the reproductive toxicity potential of a "prototype" vaccine may have been assessed and the similarity between the "prototype" vaccine and a new investigational vaccine(s) may have been established in terms of the manufacturing process, product characterization and clinical safety, additional reproductive toxicity studies using the final clinical vaccine formulation may be necessary (e.g., 9 versus 11-valent pneumococcal conjugate vaccine; multivalent versus monovalent GBS vaccine). [Note that in CDER, reproductive toxicology studies are usually performed for every new "molecular entity", with only few exceptions.]

Reproductive toxicity studies should be performed for all vaccines that belong to a similar class (e.g., polysaccharide vaccines), but which contain components derived from different organisms, or where different manufacture and/or purification procedures are employed.

Use of mercury containing preservatives in vaccines intended for maternal immunization:

The FDA Modernization Act (FDAMA) of 1997, Section 413 (c)(2), states that "...regulations shall be designed to protect the health of children and other sensitive populations from adverse effects resulting from exposure to, or ingestion or inhalation or mercury."

For investigational vaccines indicated for maternal immunization, the use of single dose vials should be required to avoid the need of preservative in multi dose vials as required by the Code of Federal Regulations (CFR). Of concern here is the potential neurotoxic effect of mercury especially when considering cumulative doses of this component early in infancy. All mercury-containing vaccine formulations should be evaluated in appropriate preclinical reproductive toxicology studies that include the assessment of postnatal behavioral and developmental endpoints (This topic is being addressed by the FDA-wide working group on mercury-containing drugs).