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International Life Sciences Institute

6578 '01 JAN 23 P2:37

December 6, 2000

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Rom 1061
Rockville, MD 20852

Re: Docket #00D-1400

Dear Sir or Madam:

The Immunotoxicology Technical Committee (ITC) of the ILSI Health and Environmental Sciences Institute is pleased to provide the enclosed comments on the FDA Center for Biologics Evaluation and Research's "Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications," in response to your September 8, 2000, request for comments in the *Federal Register* (F.R. Vol 65, #175). The ITC appreciates the opportunity to contribute to the scientific discussion around this issue.

The ILSI Health and Environmental Sciences Institute (HESI) was established in 1989 as a global branch of the International Life Sciences Institute, a nonprofit, worldwide foundation, to provide an international forum to advance the understanding of scientific issues related to human health, toxicology, risk assessment and the environment. By bringing together scientists from academia, government, and industry, HESI seeks a balanced approach to solving problems with broad implications for the well-being of the general public. Guided by its Board of Trustees, the institute contributes to the identification and resolution of health and environmental safety issues of mutual concern through the support of scientific research and other activities.

Please direct any comment or questions concerning this document to Mr. David Sandler, HESI Senior Project Manager, at 202/659-3306, or dsandler@ilsi.org.

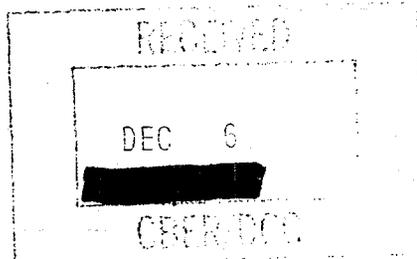
We hope that our comments will be helpful to FDA in finalizing this Guidance document.

Sincerely,



Denise E. Robinson, Ph.D.
Executive Director

Enclosure



00D-1400

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International Life Sciences Institute

**Comments
on the
Draft Guidance for Industry
Considerations for Reproductive Toxicity Studies for
Preventative Vaccines for Infectious Disease Indications
(U.S. Food and Drug Administration
Center for Biologics Evaluation and Research)**

Overall Comments:

The guideline is well written and provides flexibility for scientific judgment in the design of the study. Although the immunologic endpoints are scientifically interesting, some of them may be more appropriate for tier 2 testing once a developmental toxicity has been identified, and/or they are technically challenging and may not be reasonably feasible.

Specific Comments:

IV. A. General Considerations

1. We agree that each product needs to be evaluated on a case-by-case basis and an early dialogue needs to be initiated with CBER to reach an agreement on study design and endpoints.

IV. B. Specific Considerations

B 1 and 6 - Immunologic Parameters and Follow-up Period

1. An extensive evaluation of the immune response to the vaccine is requested in the dams, fetuses, and newborns, including assays for milk antibodies.
2. We agree that it is generally important to demonstrate an immune response to the vaccine in the dam to demonstrate exposure.
3. At times, it may also be helpful to determine if the antibody response is present in the newborn at the time of birth as well as at the end of lactation (i.e., to non-quantitatively verify exposure).
4. However, in the absence of toxicity over a wide exposure range, it seems unnecessary as a first-tier test to determine the following:
 - a. whether the response was passive (transferred from the dam) or active (developed in the fetus);
 - b. how the response was transferred (cord blood or milk);
 - c. the kinetics/persistence of the response in the newborn;
 - d. the potential tissue cross-reactivity of the response in the fetus.
5. Overall, these tests would be more appropriately conducted as a second-tier evaluation to better understand the mechanism of any developmental toxicity observed.

6. If the antibody response generated has an adverse effect on the pup, then it should be detected as would any adverse effect (e.g., viability at birth, postnatal survival, growth, function, and fetal variations/abnormalities) caused by any other conventional drug.
7. It would be difficult to determine the kinetics of the response in the pups, as one litter will be required for each time point in order to obtain enough serum. To achieve an acceptable study design, the group size would have to be enormous.
8. It would also be technically very challenging to assess tissue cross-reactivity of the response in the fetus, especially since this must be determined using sera obtained from the same species, potentially creating high-background issues. However, it may be worth considering as a tier-2 evaluation.
9. There are no "acceptable" or "validated" assays for measuring immune function in newborn, young animals or other immature animals. Only "validated" work has been in adults.

B. 2. Animal Models

1. We concur that only one species may be necessary for reproductive (teratology) toxicity testing and that the species should be able to mount an immune response to the vaccine, if possible.
2. If a non-traditional species is used, how much "historical control" data will be acceptable to the agency? It will likely be very limited, especially in a newborn.

B. 3. Dose

1. Why is it necessary to be at least 15-fold greater than the human dose on a mg/kg basis?

B. 4. Schedule

1. We agree that the immunization schedule should be based on either the clinical schedule or on the kinetics in that species.

B. 5. Exposure Period

1. This section leaves the impression that a Segment I study (covering ICH stages A and B) is not required and that postweaning follow-up in the pups through reproductive maturity (covering ICH stage F) is also not needed. We concur with this statement for routine testing. However, this point needs to be more clearly made in the guidance. Also, the document should not refer to reproductive toxicity but rather to embryo-fetal toxicity.

B. 7. Endpoints

1. It is unclear whether some of the endpoints are consistent with ICH reprotoxicity guidelines. For example, "Postnatal development may include maternal-newborn relationship, neonatal adaptation to extra-uterine life..." are not terms used in the ICH guidelines and therefore should be renamed for consistency. Also, "crown-rump length" is not an ICH-required endpoint in any reprotoxicity study design. The document should use wording used in ICH guidelines, unless not appropriate.