

# Bristol-Myers Squibb Pharmaceutical Research Institute

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December 4, 2000 <sup>9 8 12 '00</sup> DEC -7 19:36

**Dockets Management Branch  
Food and Drug Administration, HFA-305  
5630 Fishers Lane, Room 1061  
Rockville, MD 20857**

**Re: Docket No. 00D-1400; Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventative Vaccines for Infectious Disease, Reference to 65 Federal Register 175 (September 8, 2000)**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1999, pharmaceutical research and development spending totaled \$1.4 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventative Vaccines for Infectious Disease.

## Summary of BMS Comments on Proposal

We commend the U.S. FDA for their consideration of the potential effects of preventative vaccines on embryo-fetal development. We concur with their concerns and believe that developmental studies should be considered with preventative vaccines. However, many of the immunological endpoints are more appropriate for tier 2 testing once a developmental toxicity has been identified, and/or they are technically challenging and not reasonably feasible. Specific comments are cited below.

00D-1400



A Bristol-Myers Squibb Company

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## Specific Comments

### **IV. A. General Considerations**

- 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**

- An extensive evaluation of the immune response to the vaccine is requested in the dams, fetuses, and newborns, including assays for milk antibodies.
- We agree that it is generally important to demonstrate an immune response to the vaccine in the dam to demonstrate exposure.
- 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).
- However, in the absence of toxicity over a wide exposure range, it seems unnecessary as a first-tier test to determine the following:
  - whether the response was passive (transferred from the dam) or active (developed in the fetus);
  - how the response was transferred (cord blood or milk);
  - the kinetics/persistence of the response in the newborn;
  - the potential tissue cross-reactivity of the response in the fetus.
- Overall, these tests would be more appropriately conducted as a second-tier evaluation to better understand the mechanism of any developmental toxicity observed.
- 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.
- It would be pragmatically very challenging 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. Therefore, group size would have to be enormous.
- 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.

#### **B. 2. Animal Model**

- 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.

#### **B. 3. Dose**

- Why is it necessary to be at least 15-fold greater than the human dose on a mg/kg basis? Why would 10-fold not be sufficient?

#### **B.4 Schedule**

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

#### **B5. Exposure Period**

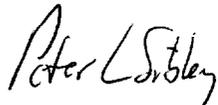
- This section leaves the impression that a Segment I study (covering ICH stages A and B) is not required and that postweaning follow-up in the pups through reproductive maturity (covering ICH stage F) is also not needed. We concur with this statement for routine testing. However, this point needs to 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**

- It is unclear whether some of the endpoints are consistent with ICH reproduction-toxicity 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 reproduction-toxicity study design. The document should use wording used in ICH guidelines, unless not appropriate.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Peter L. Sibley, Ph.D.  
Vice President, Drug Safety Evaluation  
and Veterinary Sciences

Sincerely,



Laurie F. Smaldone, M.D.  
Sr. Vice President, Regulatory Science  
and Outcomes Research

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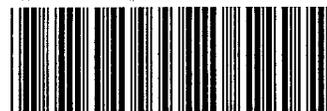
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