

SB
SmithKline Beecham
Pharmaceuticals

N.A. Regulatory Affairs
Vaccines and Oligonucleotides

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December 6, 2000

Dockets Management Branch (HFA-305),
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: Comments on Draft Guidance [Docket No. 00D-1400]

Reference is made to the Food and Drug Administration's Draft Guidance entitled "*Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications*" issued in the Federal Register Vol. 65, No. 175 Friday September 8, 2000 and the call for all comments by December 7, 2000.

SmithKline Beecham Pharma has reviewed this document and at this time respectfully enclose our comments for your consideration.

Should you have any questions regarding the enclosed or require any additional information, please do not hesitate to contact me by telephone at 215-751-6324 or by fax at 215-751-4926.

Yours Sincerely,



P. Kala Agarwal, M.Sc.
Assistant Director
North American Regulatory Affairs

cc: Dr. Johan Van Hoof, SBB

00D-1400

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Manufacturer's Comments – *Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications* [Docket No.: 001D-1400]

Section of Guidance	Comments
I. Introduction	<ul style="list-style-type: none"> ▪ Title of the document is somewhat broader than the scope of the document, as classical reproductive toxicity studies include studies to assess the impact on fertility (Segment 1)
II. Definitions B. Reproductive Toxicity III. Vaccine target population and timing of pre-clinical reproductive toxicity studies	<ul style="list-style-type: none"> ▪ Along the lines of the above comment, the definition in Section II of Reproductive toxicity would cover Fertility studies (Segment 1) however the footnote referenced states that the present document does not address concerns regarding male reproductive toxicity and fertility studies. This taken with the statement made in Section III, in the last paragraph, where it mentions the possible need for male fertility studies for certain products makes it clear that this document is not intended to cover male fertility studies. We would like to suggest that additional guidance on the aspect of female fertility studies be provided
I. Introduction IV. Design of Reproductive Toxicity Studies A. General Considerations 3 Application of ICH Guidance document S5A	<ul style="list-style-type: none"> ▪ Based on the title and both of these sections it is can be understood that that this document does not include therapeutic vaccines. However as many therapeutic vaccines under development will be intended for use in adolescents and adults, SB requests clarification how this document may be applied to therapeutic vaccines and reference to other guidances meant to cover specifics to therapeutic vaccines (i.e. therapeutic vaccines do not always have a relevant animal model in order to conduct the studies).

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Section of Guidance	Comments
IV. Design of Reproductive Toxicity Studies	<ul style="list-style-type: none"> ▪ The guideline covers vaccines intended for maternal immunization (pregnant women) and unintentional/inadvertent vaccination (where pregnancy begins during the timeframe of immunization), the depth of the investigations (read-outs, follow-up of offspring) can be expected to be different in both situations and SB suggests that this be recognized in this guideline
III. Vaccine target population and timing of pre-clinical reproductive toxicity studies	<ul style="list-style-type: none"> ▪ It is indicated that studies can be submitted to the BLA if they have not previously been submitted to the IND – this implies that if the studies are submitted to the IND that they are not required to be submitted in the BLA, however FDA Form 356h requires that preclinical information including reprotoxicity be included in the BLA even if they are already submitted to the IND. SB requests clarification on this administrative procedure.
II. Definitions C. Developmental Toxicity	<ul style="list-style-type: none"> ▪ This defines development toxicity including "effects induced or manifested postnatally." It is suggested that guidance be provided for the time period up to which the off-spring should be observed, and also specify the end of the postnatal period for the most frequently used species.

Section of Guidance	Comments
<p>IV. Design of Reproductive Toxicity Studies B. Specific Considerations 1. Immunological Parameters</p>	<ul style="list-style-type: none"> ▪ This section mentions the "Potential of the vaccine to induce immunopathological effects (i.e. development of antibodies cross-reacting with the fetal tissues and auto-antibodies or other responses) should be assessed". It is also suggested that "such evaluation may include an examination of fetal tissue for potential cross-reactivity with passively transferred antibodies induced by immunizing the pregnant animal..." SB believes that reprotoxicity studies should not include specific studies on the induction of cross-reacting epitopes, and in fact routine read-outs (e.g. histopathology of major organs) included in teratogenicity studies are more relevant to detect malformations or other negative impact on the fetus. As long as no effects are observed in these read-outs, further investigations are of little added value. ▪ This section also mentions the need to assess the "presence, persistence and effects of antibody response in the newborn". SB believes that studying the "persistence" of the immune response is generally not necessary especially in case of inadvertent exposure. Should there be a rationale to study this generally, the document should provide guidance on how long-term kinetics should be followed. The study of the effects of antibody response is considered part of the histopathological analysis of the newborn and presence of antibodies is generally checked for as well.

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Section of Guidance	Comments
IV. Design of Reproductive Toxicity Studies B. Specific Considerations 3. Dose	<ul style="list-style-type: none"><li data-bbox="981 409 1968 865">▪ This section mentions the need to include a dose-range in the reprotoxicity studies. SB does not believe a dose-range in a reproductive study is warranted provided the administered dose induces an immune response in the selected animal species and the dose administered exceeds the human dose on a mg/kg basis (e.g. 15 times the human dose). The definition of an appropriate dose (i.e. one that induces an appropriate immune response) could be conducted in a separate experiment in non-pregnant animals. This is particularly the case for vaccines that are not intended to be administered to pregnant women, where the main purpose should be to document the absence of teratogenic effects.

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Section of Guidance	Comments
<p>IV. Design of Reproductive Toxicity Studies B. Specific Considerations 6. Follow-up Period</p>	<ul style="list-style-type: none"> ▪ This section mentions the need for a follow-up period during which the persistence of antibodies in the off-spring is followed, the potential interactions of these antibodies with host tissues and the presence of antibodies in the milk. In general the guideline document should provide guidance on the expected time period of follow-up. ▪ SB questions the relevance to study antibody persistence in the off-spring, especially for vaccines not intended to be given to pregnant females. If such a follow-up would be recommended, guidance would be needed on how long this should be. ▪ With respect to the potential interactions of antibodies in the off-spring with host tissues, SB believes such an analysis does not add anything provided there are no anatomical malformations or no impact on histopathology of major organs at weaning. ▪ With respect to the presence of antibodies in milk, SB believes that such an analysis is of limited applicability for vaccines not intended to be given to pregnant females. In these cases inadvertent vaccination of the mother will be limited to one dose of the vaccine, early in pregnancy, which is a situation quite different from the vaccination schedule used in the reprotoxicity studies.

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Section of Guidance	Comments
V. Vaccine Product Class	<ul style="list-style-type: none"><li data-bbox="985 448 1962 685">▪ This section mentions that studies need to be performed for every final clinical vaccine formulation used in studies that enroll pregnant women. The types of changes made to product, which would require additional study would need to be defined – there are several changes that are made to product during clinical development and not all of them should require additional study.

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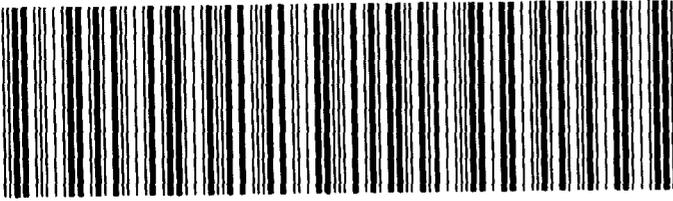
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