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Food and Drug Administration
HFA-305
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**Re: NAS 0; Not Product Specific
Response to FDA Request/Comment: Draft Guidance for Industry on
Clinical Lactation Studies - Study Design, Data Analysis and
Recommendations for Labeling
[Docket No. 2005D - 0030]**

Dear Sir or Madame:

Enclosed please find comments from GlaxoSmithKline on the 'Draft Guidance for Industry on Clinical Lactation Studies - Study Design, Data Analysis and Recommendations for Labeling.' We appreciate the need for clinical pharmacology data in lactating women and welcome the FDA initiative to provide a guidance document. GSK has general comments about the purpose and scope of the proposed guideline, as well as the studies that would be required to generate clinical data in the maternal and infant populations. Specific comments are also provided, organized under the same section headings as used in the draft guidance and cross-referenced by line number.

This submission is provided in electronic format according to the instructions provided at <http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm?AGENCY=FDA>.

Please contact me at (919) 483-6405 if you require clarification or have questions about these comments. Thank you.

Sincerely,

A handwritten signature in black ink that reads 'Anne N. Stokley'.

Anne N. Stokley, M.S.P.H.
Director, Policy, Intelligence & Education
US Regulatory Affairs

Comments on Draft Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling

GENERAL COMMENTS:

1. We appreciate the need for clinical pharmacology data in lactating women and welcome the FDA initiative to provide a guidance document. Since the presence of a drug in breast milk does not necessarily indicate a health risk for the breast-fed child, we agree with the Agency's recommendation for a step-wise approach in conducting such clinical studies. Simpler, clinically feasible lactation studies such as the "Lactating Women (Milk Only)" study may provide adequate information in assessing the extent of the passage of the drug into breast milk and allow appropriate assessment of the potential health risk for the breast-fed child. Based on the kinetics of drug in the milk, appropriate preventive measures can then be adopted to minimize exposure to drug in breast milk.
2. The more complicated study design such as the "Mother-Infant Pair" design, although perhaps providing additional information, would be very difficult to conduct clinically in such a patient population using a multiple PK/PD sampling scheme with an appropriate sample size. This may be detrimental to the overall goal of obtaining scientific information in lactating women.
3. The draft guidance states and/or implies on Lines 68 and 142 that nearly all drugs could be potentially used in lactating women. However, requiring lactation studies for all which drugs could be used by lactating women is not practical for several reasons. In general, lactating women and infants should not be exposed to a new chemical entity until sufficient safety data have accumulated – typically several years after commercial approval. Mandating such studies for all drugs may not be practical for drugs which are not likely to be used in lactating women, and would create an unnecessary burden on the availability of clinical sites for potential subjects.

SPECIFIC COMMENTS:

1. 'Serum' and 'plasma' have been used interchangeably throughout the guidance. This may need to be clarified.
2. Section III (*Considerations for when to conduct a clinical lactation study*, Lines 150-151) – Consider expanding this paragraph to include other situations in which lactation studies are not needed: drugs with low bioavailability, drugs with very short elimination half-lives (< 1 hour) and low volumes of distribution, and certain disease conditions (e.g., HIV, malaria) for which clinical lactation studies are not recommended.

3. Section III (*Considerations for when to conduct a clinical lactation study*, Lines 153-155) – The draft guidance states that post-approval information on experiences in lactating women should routinely be submitted to the Agency. Please provide more clarity on what information the Agency is requesting.
4. Section III (*Considerations for when to conduct a clinical lactation study*, Lines 171-174) – The non-clinical models should also refer to animal studies. This section may need to be expanded further to discuss the role of non-clinical models which form the basis for prediction to humans. Current literature reviews convincingly show the value of using a combination of *in vitro* experiments and *in vivo* studies in animal models to determine whether a drug will have a high exposure to milk in women. In certain cases, this information in conjunction with other clinical pharmacological data generated in humans (males and females) may assist in deciding whether to conduct a clinical lactation study. It may also help in selecting the type of clinical study that should be conducted.
5. Section IV (*Study Design Considerations*) - The order of study design needs to be reversed to be consistent with the step-wise approach in clinical development - (i) Lactating Women (Milk Only), (ii) Lactating Women (Plasma and Milk) and (iii) Mother-Infant Pair Design.
6. Section IV (*Study Design Considerations*, Line 197) – This section suggests that a single-dose study may be sufficient for drugs that don't accumulate with chronic dosing. However, if drug distribution and equilibration into milk does not occur rapidly, then a single-dose study may provide false assurance of low distribution into breast milk. Single-dose studies are most appropriate for drugs which are generally given as a single-dose (p.r.n. administration or single-dose therapies).
7. Section IV (*Study Design Considerations*, Lines 235-239 and Lines 263-266) – The listed characteristics are not comprehensive and some appear quite vague. The basis for potential accumulation in breast milk, and likelihood of being well absorbed by the breast-fed child needs to be clarified. Other characteristics such as plasma and milk protein binding, molecular weight, mechanism of transport, degree of ionization, and clearance pathways may need to be specified.
8. Section IV (*Study Design Considerations*, Line 246 – This section notes that effects on milk composition should be considered. Further guidance on this type of study should be given since many factors other than drug use can affect milk composition (see possible confounders noted on lines 326-335, and line 383).
9. Section IV (*B.2. Lactating Women (Milk Only)*, Lines 281-283) – May consider the need to define “cut-off” value for “low” drug amount in milk that precludes need for further studies. Arbitrary safety limit for drug exposure in breast milk is <10% of the weight adjusted maternal dose (could specify for broad therapeutic index drugs only).
10. Section IV (*C. 3. Study participants*, Lines 337-339) – The role of drug efflux and transporters as well their polymorphic characteristics should also be included as factors that may facilitate drug secretion into milk via an active transport mechanism.

11. Section IV (*C. 6. Sample Collection and Analysis*, Lines 388-389) - Special handling and storage of milk samples may need to be provided to prevent any degradation of human milk samples.
12. Section V (*A. Parameter Estimation*) - Lines 470-472 could be moved forward and inserted in Line 404 under Section IV.C.6. when discussion about measuring total and unbound concentrations appears for the first time in the guidance. Also, note that Line 403 is inconsistent with line 462 on whether unbound drug concentrations should be measured in milk samples.
13. Section VI (Labeling) - In situations where nonclinical or clinical lactation studies may support contraindicating a drug during breast-feeding, the Agency should consider including "Contraindications" under "Labeling".
14. Section VI (Labeling, Lines 627-633) – This section suggests that the Special Populations section of the label would include data on drug transfer into breast milk, potential exposures in infants, etc. Recommend that this information be located in the Precautions, Nursing Mothers section of the label. The information in the Special Populations section should be limited to changes in the pharmacokinetics of the drug in lactating women (i.e., overall elimination half-life, AUC, etc). Therefore, the proposed text in Lines 655-663 would appear in the Precautions, Nursing Mothers section of the label.
15. Section VI (Labeling) - Recommend that the information represented on Line 674 and Line 689 be presented in the Special Populations section of the label.
16. Section VI (Labeling, Lines 693-704) - Recommend that if lactation does not significantly influence the pharmacokinetics of a drug, that statements regarding lactation in the Dosage and Administration section of the label would be unnecessary.
17. Section VII (Considerations for Future Research) – This section may be included under Section II (Background) with detailed discussion on the role and predictive value of these approaches used routinely in early clinical development.
18. Bibliography – The Agency should consider updating all the references to reflect numerous recent useful publications in this field (specially American Academy of Pediatrics recommendations regarding use of drug in breastfeeding women, 2001).
19. The Agency should consider providing list of drugs that are currently (i) contraindicated during breast feeding, and (ii) known to be compatible with breastfeeding. The recommendations by the American Academy of Pediatrics may be very valuable in this regard.