



Global Research & Development

January 14, 2005

Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, Maryland 20852

Re: **Draft Guidance for Industry on Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling**
[Docket No. 2004D-0459, 69 *Federal Register*, 63402-63403, November 1, 2004]

Dear Dockets Management:

Pfizer Inc submits these comments on the Draft Guidance for Industry on Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling, published in the *Federal Register* on November 1, 2004.

Pfizer appreciates the opportunity to provide comments on this draft guidance in this area of clinical pharmacology.

General Comments:

As noted in the guidance, pregnant women needing to take medications are a population that presents a real challenge to the safe conduct of clinical trials. As such, we support the development of an FDA guidance to promote scientifically and ethically sound approaches to studying safe and effective use of medications important in medical management of pregnant women.

This guidance provides a very broad overview to this complex topic and does a good job of capturing the issues. However, the introduction states that the FDA is not providing guidance on how or when to conduct these trials (lines 34-36). From that perspective, how would Sponsors determine if their study approach would even be acceptable if, for example, it was deemed important to include information about use in pregnancy in a label? There are more specific details that are still required for Sponsors to make informed judgments on when to consider such studies. In particular, we suggest that more detail is needed on:

- 1) Whether all drugs should to be evaluated, and
- 2) What the expected timing is of such studies in a drug development program. The draft guidance currently states (line 138) that the FDA anticipates these studies to be completed in the post-marketing phase, though this might not always be the case.

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Important to the understanding of the challenges of these types of studies are the different circumstances under which pregnant women would be faced with a decision about taking medication. The benefit/risk for these decisions can vary. The information on the use of medications during pregnancy (lines 47 – 61) would benefit from comments on the risks of (a) treatment of acute and chronic conditions occurring with significant frequency in pregnant women; (b) treatment of pregnancy-related conditions and c) the risks associated with non-treatment of the disease or condition.

The guidance should be made clearer on issues of patient access and follow up. Finding women in the first trimester would be challenging, as selection and pre-screening activities often need to be started before pregnancy is confirmed. Studies in the first trimester pose a particular challenge for the safe conduct of trials because of high potential risk during the critical period of organogenesis both from the standpoint of drug exposure and the potential complications of multiple assessment procedures. Evaluation of the first trimester would benefit greatly from use of all available PK/PD modeling approaches.

The longitudinal studies proposed for chronically given drugs pose another challenge, as the guidance refers to the need to assess the PK through 1st and 2nd trimesters, then later it states that changes through all three trimesters, and also post partum, should be assessed (Section IV A). There may be reluctance on the part of the enrolled patient to undergo PK/PD assessment through all of these periods. The requirement to make PK/PD assessments over the duration of pregnancy for drugs with potential therapeutic benefit also poses questions of dosing frequency relative to the determination of minimal risk – it is implied that only single dosing is suitable for non-therapeutic benefit. It is suggested that the guidance provide more examples on how to determine minimal risk for both the patient and the fetus in keeping with current guidelines on the ethical conduct of clinical trials.

With this in mind, we recommend that a decision tree be included in the guidance that details the critical factors to be considered when determining if and when a study in pregnant women would be warranted. Given the indication being developed, for example, will the drug be used by women who may become pregnant and for medical reasons wish to continue with the drug's use, or will the drug be used primarily to treat women in pregnancy and is a drug for specific use in pregnancy. The tree should also elaborate on timing of the assessments during pregnancy and the perinatal period as well as various approaches that might be applied for studying PK in these situations. These decisions should then form the basis of discussions for potential studies be held at the appropriate Regulatory/Sponsor meeting [such as EOP2]. Finally, further consideration is needed regarding the importance of specific guidance(s) for recombinant versions of hormones that are crucial for fetal development (eg. EPO, leptin).

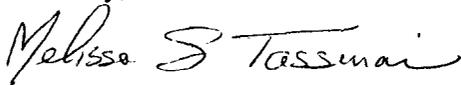
Specific comments:

We have also provided some specific comments to the draft guidance detailed below for your consideration:

Line	Comment
95	Concurrent changes in alpha-1-acid glycoprotein should be mentioned
145-149	To what extent has the use of the PSUR to collect information been a useful approach to determine whether a PK study should be conducted in pregnant women? It would be useful if some examples could be provided.
224	It should be recognized that it might not be necessary or feasible to get post-partum data at all if the drug is predominantly prescribed during pregnancy. Suggest adding the phrase 'as appropriate' to the last sentence.
249 – 251	In other settings, a POP-PK approach has been sufficient for identifying covariates and should be considered an appropriate approach rather than only a preliminary step.
321-23	Suggest deletion of this sentence. The guidance suggests that lower or less frequent doses may minimize fetal risk. This is an assumption. This doesn't seem like a scientifically sound approach for determining the starting dose for a drug already on the market. The next sentence (323-25), however, is more appropriate, i.e. Dosage regimen can be adjusted based on best available pre-study estimates of the PK of the drug and its active metabolites and what is known about drug elimination.
335	Urine samples should only be collected as appropriate (eg not usually informative for biologics)
414	All discussion re development of dosing recommendations concerns PK assessment. If PD samples have been collected, can these also be used for dosing recommendations? The guidance should indicate potential outcomes if, for example the PK is different but PD does not change.

We thank you for this opportunity to comment and would invite direct dialogue with the Agency if you would consider the opportunity valuable.

Sincerely,



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Senior Director
Pfizer Global Research and Development