

PHARMACIA

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Jenny Peters
Director
Global Regulatory Affairs
Global Regulatory Policy & Intelligence

Pharmacia Corporation
7000 Portage Road
Kalamazoo, Michigan 49001

telephone: (616) 833-8141
facsimile: (616) 833-0512
jenny.l.peters@pharmacia.com

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

Re: Docket No. 99N-2079
*Reviewer Guidance - Integration of Study
Results to Assess Concerns about Human
Reproductive and Developmental Toxicities*

Dear Sir/Madam,

Pharmacia appreciates the opportunity to review the draft guidance "*Integration Of Study Results To Assess Concerns About Human Reproductive and Developmental Toxicities.*" We applaud the efforts of the FDA to establish an objective approach to evaluating reproductive toxicity data.

We have also reviewed and agree with the comments submitted by the Reprotoxicity Technical Group of PhRMA. We would like to emphasize the following two points from those comments.

Line 34. Nature of the adverse response

While the guidance states that it is not intended to consider the nature of the adverse response, the nature of the response is a critical component in evaluation of risk for a specific finding. It is recommended that FDA consider PhRMA's suggestion to give additional weight to signal strength.

Lines 776-786. Summary/integration of positive findings

We concur with PhRMA's recommendation that having as an end result a summary narrative applicable to a labeling risk statement would allow for flexibility in judgment and for the crafting of a rationally-based risk assessment.

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Additionally, we would like to add the following comments:

Line 129. Mortality

Abortion has been classified as a developmental effect. There may, however, be circumstances in which abortion may be the result of a reproductive toxicity, as is the case with a number of abortive agents. Therefore, abortion could be classified as both a reproductive and a developmental toxicity.

Line 565. Definition of ED90

It should be noted that in some therapeutic areas the ED90 is defined as the dose causing 90% efficacy in the experimental model (eg, antitumor effect, reduction of a target signal, etc). Perhaps the ED90 as defined could be given as one example of an appropriate endpoint.

Lines 627-631. Comparisons of drug distribution profiles

It is mentioned that tissue distribution in humans should be compared with that in animals in the evaluation of the risk. In how many cases will the placental transfer in humans be known, and especially how often will the target tissue concentration in human embryos be known? If this information is not frequently available, what is the rationale for including this as an endpoint in the guidance document?

Appendix A. Sample scenarios

In the light of the very detailed dissection of classes and signals, the sample scenarios given in Appendix A seem overly simple. A more complex example could be presented that would include working through the step-wise integration process depicted in Figure C.

We thank you for the opportunity to comment on this draft guidance. Please let us know if you have any questions on our review.

Sincerely,

A handwritten signature in black ink, appearing to read 'Jenny Peters', with a stylized, flowing script.

Jenny Peters

PHARMACIA & UPJOHN INC
BLDG 295 NY
7000 ROYALTE MI

KALAMAZOO MI 49001

TINA HIRSH 616-35-1497

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Fed + Drug Administration
5630 Fisher Lane Room 1461
Rockville MD 21152
Dept + 1100 F Branch HFA 3LS

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