

11 March 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20952

Dear Sir or Madam:

RE: Draft Guidance for Reviewers on the Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities
Docket No.99N-2079

Members of the Teratology Society, a multidisciplinary scientific society founded in 1960, study the causes and biological processes leading to birth defects. Among its many activities, the Teratology Society addresses public health issues regarding the causes and prevention of birth defects and developmental disabilities. We are writing to comment on the above-named Draft Guidance [<http://www.fda.gov/OHRMS/DOCKETS/98fr/992079gd.pdf>] issued by the Food and Drug Administration on November 13, 2001 [*Federal Register* 66(219):56830-56831.]

Writing a guidance document to assist reviewers in their analysis of preclinical reproductive and developmental toxicity data is very helpful. We congratulate the FDA on recognizing the diverse nature of reproductive and developmental toxicity and the need to consider all relevant information from the broad range of studies conducted to assess the safety of a new drug. More specifically, we believe that the following aspects of the proposed process are very useful and should be part of the assessment of every drug:

- Requiring evaluation of developmental and reproductive toxicity data from animal experiments in the context of human risk;
- Requiring an explicit assessment of risk for each of 7 aspects of developmental and reproductive toxicity; and
- Explicit consideration of each of the factors that may affect interpretation of the various signals.

However, we strongly disagree with the proposed integration process. There is no scientific basis for using an algorithm to replace nuanced judgement on a case-by-case basis. Assigning a value of -1, 0, or +1 to each factor and then adding these values [p. 18, #3] does not make sense. Using a 3-point scale to characterize each factor dramatically decreases the information that is available to make subsequent decisions. Moreover, the scientific value of the carefully considered weight-of-evidence approach proposed for each factor in the primary data analysis is debased by application of a process that assumes the equivalence of factors in any single class. The factors are not of equal importance, and their relative significance is likely to vary greatly from case to case. In some instances, one of them may trump all of the others. For example, the presence of a class alert in humans or a lack of concordance between the experimental system and humans could easily be more important than all of the other factors put together. Any algorithmic approach that involves subjective scoring and addition of the values obtained is likely to be misleading in many cases. Moreover, the use of fixed cutoffs to distinguish between risk categories is completely arbitrary.

The proper approach to integration is the one advocated in the document for evaluation of the level of risk related to each factor, viz., “the analysis should reflect the weight of

evidence taking into account the quality and type of data under consideration for each factor (i.e., should not be merely an arithmetic summation of the contributory elements for each factor)” [p. 18, #2]. We recommend that the proposed integrated assessment tool be replaced by an integrated evaluation of developmental and reproductive toxicity performed on a weight-of-evidence basis at every step, taking into account the quality and type of data under consideration.

Although the introduction [p. 1] separates the process of hazard identification, with which this Draft Guidance is largely concerned, from a subsequent process that will be used to write the product label, this separation is not maintained in the document. Several recommendations are made for how the outcome of the process described should be incorporated into product labeling, even to the point of providing specific examples of proposed wording. We are, therefore, concerned that the “summary risk statement” produced as the output of the integrated assessment tool will find its way into the product label despite the fact that this statement does not take into account “the nature of the adverse response, or otherwise consider the clinical implications of the response” [p. 1, lines 34-36]. The use of such language in the label would cause considerable confusion because patients and their health care providers will vary widely in how they distinguish, or fail to distinguish, between treatments that are “predicted to increase risk” and those that “may increase risk”.

Even if the language of the proposed integrated assessment tool’s summary statements is not used directly in product labeling, it is far from clear how subsequent regulatory decisions could appropriately make use of these summary statements without taking the quality and type of data on which they are based into consideration. We recommend that “summary statements” made at intermediate stages of the assessment process be unambiguous and acknowledge the limitations of the underlying data.

We are also concerned about the limited consideration given to human data in this process. Human data are completely ignored when animal data are negative or inadequate. Human data are briefly considered when the animal data suggest a risk, but there is no indication of how the human data should be used, except as a class alert. This violates the principle that what is most important is the actual risk of developmental and reproductive toxicity *in humans* who are treated with the drug. Moreover, the process provides no incentive – in fact, there is a disincentive when the animal data suggest that there is not a risk – to collect human reproductive and developmental toxicity data after the drug has been approved. This is inherently unscientific because knowledge is always incomplete and scientific understanding requires that relevant new information be incorporated as it becomes available. Although opportunities to collect human developmental and reproductive toxicity data are usually extremely limited before a drug is approved, it is often possible to obtain such data after the drug is marketed. We recommend that assessment of the developmental and reproductive toxicity of every drug be seen as an ongoing process, not one that ends when the drug receives initial FDA approval. The process should encourage collection of human reproductive and developmental toxicity data after the drug has been approved and include provision for regular re-evaluation of all available data, and especially of relevant human data, as they become available.

Like the FDA, the Teratology Society seeks to prevent the occurrence of birth defects and developmental disabilities that result from drug treatments. We appreciate being

able to comment on the draft Reviewer Guidance and would welcome the opportunity to assist you in revising it.

Sincerely,

**J. M. Friedman, MD, PhD
President, Teratology Society**