

April 25, 2002

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

*Submitted electronically and via facsimile*

Re: Docket No. 0128258 (in association with docket no. 99N-2079), Draft Guidance for Reviewers on the Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities

These comments are submitted in response to a November 13, 2001, *Federal Register* notice inviting additional information and feedback regarding the Food and Drug Administration's (FDA) draft guidance identified above. People for the Ethical Treatment of Animals (PETA) and our over 750,000 members and supporters and Earth Island Institute and its 100,000 members are concerned that FDA health effects assessments of drugs and other substances continue to rely heavily on the results of extremely crude and cruel animal poisoning tests, none of which have ever been formally validated to establish their reliability or relevance to human health effects. The reproductive and developmental toxicity studies discussed throughout the guidance document typify this situation.

These comments stress the need to substantially improve the science behind FDA health effects assessments and, in particular, the critical importance of (1) proper test method validation according to internationally accepted criteria, (2) devoting FDA resources, both human and financial, to "fast-tracking" the development, validation, and/or incorporation of non-animal test and testing strategies, and (3) reducing the FDA's reliance on animal testing, the reliability and relevance of which are marginal at best.

#### **VALIDATION**

The FDA is represented on the U.S. Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM), which suggests a level of understanding and interest in the proper validation of toxicological test methods that is certainly not reflected in the draft guidance document. Indeed, despite paying lip service to the issue of relevance, the guidance document makes no mention whatsoever of proper validation in relation to the tests that are required or carried out. The FDA's failure to insist on the use of only properly validated test methods results in the proverbial "garbage in, garbage out," as is evidenced by the frequent conclusion that risk to humans may be "unknown or not evaluable (*sic*)" using current methods (p. 6).



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Criteria for test method validation emerged from an international conference convened in 1996 in Solna, Sweden, by the Organization for Economic Cooperation and Development (OECD).<sup>1</sup> The resultant “Solna criteria” have since become *the* internationally accepted standard by which a test’s validity is judged. The FDA was represented both at this meeting and at subsequent OECD meetings and discussions on the topic of test method validation. There is therefore no excuse for the FDA’s apparent ignorance, or blatant disregard, of internationally accepted validation criteria by continuing to accept, and indeed mandate, the use of crude and non-validated animal test methods, which have never been properly evaluated to establish their reliability and/or relevance to human health effects.

## RELEVANCE

Relevance is the extent to which a test correctly measures or predicts the biological effect of interest *in the species of interest*. In the case of FDA-mandated health effects assessments, the species of interest is clearly humans, as it is doubtful that a federal agency would mandate such extensive toxicity studies in order to mitigate against adverse drug reactions in rodents. It is therefore remarkable that in the years since validation criteria have existed, no effort has been made to establish the relevance of rodent developmental and reproductive toxicity data to humans. What is perhaps more inexcusable, however, is that this new guidance continues to call, unquestioningly, for the use of non-validated animal tests, by stating that “the integration process should be based on an evaluation of a complete set of the expected general toxicology, reproductive toxicology, and pharmacokinetic studies” (p. 2, line 50).

It is widely recognized that extrapolating from one species to another is fraught with difficulties and uncertainty, as are extrapolations from high dose to low dose, from one exposure route to another, and from one exposure time frame to another. Far from providing an unequivocal assessment of chemical risks to humans, the relevance of data derived from non-validated animal tests is *always* in question, and therefore subject to vastly differing interpretations, and often, successful legal challenges. This is evident from even a cursory review of the Bureau of National Affairs (BNA) publications, as the following examples illustrate:

- Speakers at an Institute of Medicine workshop in October 2001, concluded that “current regulatory tests may not be adequate to determine whether chemicals, pesticides, and other agents cause preterm births. Parturition...works so differently in rodents than in people that tests on these animals may fail to predict preterm births.”<sup>2</sup>
- “The National Toxicology Program’s Center for the Evaluation of Risks to Human Reproduction convened an expert panel to examine available, peer-reviewed data and determine whether methanol exposure was likely to be associated with adverse reproductive or developmental effects... The panel said it was concerned that high, accidental exposures to methanol might be associated with developmental toxicity —

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<sup>1</sup> OECD. (1997). *Final Report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods*. Paris, France: OECD.

<sup>2</sup> Anon. Current tests may be inadequate to assess chemicals for birth effects. *BNA Chemical Regulation Reporter* 8-Oct-01; 25, 1510.

***assuming rodent data applies to humans... Concerning developmental toxicity, [Methanol Institute consultant, John] Clary argued the skeletal malformations and other adverse developmental effects that occurred in mice following high exposure to methanol might not be relevant to people. There are no reported cases of methanol causing developmental problems in humans, Clary said. The toxicity found in the rodent studies may be species specific.***<sup>3</sup>

The critical importance of establishing a test's relevance to the species of interest was also discussed and reaffirmed during a recent OECD validation conference in Stockholm, Sweden, which was well attended by FDA representatives, who in fact co-chaired several of the breakout sessions. Given the international consensus that now exists on this specific issue, as well as the general importance of using only properly validated test methods in hazard and risk assessments, it is imperative that this and other FDA guidance documents be amended to reflect this new consensus. In particular, ***this guidance should stipulate that only test methods that have been properly validated according to internationally accepted (i.e., Solna) criteria are acceptable for the purposes of hazard and risk assessment. All other aspects of this guidance should conform to this principle.***

#### ALTERNATIVE TESTS AND STRATEGIES

Given the exorbitant cost of animal testing — both financial and in terms of animal suffering and death — it is imperative that the FDA make every effort to significantly reduce, and ultimately eliminate, its reliance on such tests. The draft guidance document must be revised to incorporate *in vitro* and other non-animal methods into a sequential testing strategy to significantly reduce the number of animals who are killed in FDA-mandated health effects studies.

In addition, the FDA should devote substantial resources, both human and financial, to “fast-tracking” the development, validation and use of the non-animal tests and testing strategies as total replacement methods. At present, *in silico* (computer-based) methods appear to be the most promising prospects for the replacement of animals in reproductive and developmental toxicity testing. For example, the MULTICASE expert system (MCASE-ES), currently undergoing development and validation at the FDA itself reduces a compound to all possible 2 to 10-atom fragments, and identifies “structural alerts” associated with chemical reactivity. The model then applies a weight-of-evidence approach to evaluate the toxic potency of structural alerts, both individually and collectively, to determine the likelihood of toxic effects *in vivo*.<sup>4</sup>

MCASE-ES models have been developed for both reproductive and developmental toxicity endpoints. For example, a trans-species teratogenicity model has been developed by pooling extensive data from six electronic sources. These include more than 120,000 human studies, as well as over 10,000 studies in other animal species. A 106-compound FDA prevalidation study found the specificity and predictivity of the MCASE-ES teratogenicity model to be 89.7 percent

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<sup>3</sup> Phibbs, P. Panel finds ‘minimal concern’ exposure to methanol in diet, at work causes harm. *BNA Daily Environment Report* 18-Oct-01, 200, A-5.

<sup>4</sup> Benz, D. Presentation at the 22<sup>nd</sup> Annual Meeting of the American College of Toxicology. Washington, DC. 6-Nov-01.

and 83.3 percent, respectively.<sup>5</sup> Optimal levels of performance are usually obtained by using combinations of these systems. The sensitivity of these models could be further enhanced through a collaborative development and validation effort between the FDA and other regulatory agencies in the US and internationally, whose extensive databases of regulated substances could be programmed into these models in order to greatly augment the accuracy and relevance of their predictions.

## SUMMARY

Although the draft guidance document clearly establishes the FDA's interest in reproductive and developmental toxicity in humans, and stresses the critical importance of evaluating these effects "in accordance with sound scientific principles" (p. 2, line 67), the current draft does not remotely approach the achievement of these goals in a credible manner. The FDA's continued acceptance of non-validated — and clearly flawed — animal studies violates the direction given by Congress for federal agencies to implement systems of decision-making that are based on sound science, which in turn undercuts the credibility of its assessments of the health effects of drugs and other substances.

To quote Professor Michael Balls, head of the European Centre for the Validation of Alternative Methods, with regard to the use of non-validated test methods: "What would be the value of the data such tests would provide, and with what confidence could they be applied in making decisions?"<sup>6</sup> The registration of new drugs provides an excellent opportunity for the FDA to make a concerted move away from its reliance on cruel and non-validated tests methods. ***We therefore strongly urge the FDA to review and substantially revise this guidance document to incorporate a sequential testing strategy as described above, making maximum use of available in vitro and other non-animal methods, while at the same time, making every effort to eliminate the use of cruel, costly and non-validated reproductive and developmental toxicity studies in animals.***

We respectfully request your serious consideration and responsiveness to our comments. Please feel free to contact me with any questions or comments regarding this submission.

Sincerely,



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<sup>5</sup> Matthews, E. Presentation at the 22<sup>nd</sup> Annual Meeting of the American College of Toxicology. Washington, DC. 6-Nov-01.

<sup>6</sup> Balls, M. (1999). *ATLA* 27, 1-5.