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Dockets Management Branch
5630 Fishers Lane
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RE: Docket # 99N.2079

Sirs:

I would like to provide a couple of comments to the above docket concerning the draft guideline for evaluating reproductive toxicity risk, "Considerations in the Integration of Study Results for the Assessment of Concern for Human Reproductive and Developmental Toxicities". This guideline was the subject of a workshop on June 24 which I attended.

Comment #1: I was concerned to hear that the toxicologists at the FDA would not be allowed to distinguish reproductive toxicity findings that might be reversible or have minimal impact on function from changes that would not be reversible or have a major impact on function. Apparently these judgments regarding severity or impact on the organism are to be left to the clinicians at the FDA. I certainly agree that the clinicians need to make judgements about the potential clinical impact of any preclinical findings. However, in my 20 years experience in the pharmaceutical industry, I have always found that physicians/clinicians need input from toxicologists on the biological significance of most findings in reproductive toxicity studies. When major malformations are found, these usually don't require much explanation. But other findings usually do require some kind of explanation or qualification. Examples would include delayed ossification, skeletal variations such as wavy ribs or extra ribs, dilated renal pelvis due to developmental delay, delay of developmental indices to due low birth weight or delayed growth, or variabilities in behavioral data. Most clinicians do not have the training or years of experience dealing with these type of data that most toxicologists do have, and I am concerned about the overall outcome of a process that does not allow complete utilization of the expertise available from the FDA toxicologists. I would like to encourage modification of the guideline to allow expert input from the toxicologists on the expected biological impact of reproductive toxicity findings.

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Comment #2: The section on Relative Exposures (section 4.5) cites various levels of concern for relative exposure ratios (animal:human) of ≤ 10, 10-25, or ≥ 25. However, no distinction is made among the various metrics that might be used to calculate the relative exposure ratio. In other words, the same degree of concern would be generated by a relative exposure ratio (safety margin) of 10 fold regardless of whether the exposure ratio was calculated on the basis of administered dose or plasma AUC. I feel that the exposure ratio associated with a given level of concern should be adjusted for the type of metric used to calculate the exposure ratio. For example, the traditional 10 fold safety margin between no-effect dosage in animals (particularly rodents) and humans was an adjustment for the known differences in sensitivity to the effects of various chemicals in animals compared to humans. These differences in sensitivity are largely related to differences in metabolism associated with differences in body surface area/weight ratios. When one compares systemic exposure on the basis of plasma AUC, one has already accounted for differences in metabolic rates and patterns, and no further correction should be needed. (In my view, therefore, a relative exposure ratio of 1 for plasma AUC exposure at the no-effect level in animals to plasma AUC exposure at the therapeutic level in humans would be acceptable.) Similarly, the safety margin required for relative exposures calculated on the basis of administered dosage corrected for body surface area (mg/m^3) should be less (close to 1 in my view) than for relative exposures calculated on the basis of uncorrected administered dosage. I would like to encourage modification of this section to allow, for example, levels of concern of ≤ 1, 1-2.5, or ≥ 2.5 associated with relative exposure levels calculated on the basis of AUC or dosaged adjusted for body surface area/weight, and levels of concern of ≤ 10, 10-25, or ≥ 25 associated with relative exposure levels calculated on the basis of unadjusted administered dosage.

Sincerely,

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