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30 May 2002

Robert Osterberg, Ph.D.
Acting Associate Director for Pharmacology and Toxicology, CDER
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 99N-2079 (Federal Register; November 13, 2001, Volume 66, Number 219, pp. 56830-56831) "Draft Reviewer Guidance: Integration of study results to assess concerns about human reproductive and developmental toxicities."

Dear Dr. Osterberg:

On behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA), I would like to thank the Food and Drug Administration (FDA) for seeking comment on its draft Reviewer Guidance "Integration of study results to assess concerns about human reproductive and developmental toxicities." PhRMA is a trade association representing the research-based pharmaceutical industry in the United States. PhRMA member companies have more than 1000 drugs and biologics in development and invested over \$30 billion dollars in research and development in 2001. The following comments were developed by the Reprotoxicity Technical Group of PhRMA's Preclinical Safety Leadership Committee.

The consensus of the Reprotoxicity Technical Group was that the Draft Reviewer Guidance, i.e. the Integrated Assessment Method (IAM), is a well-thought out approach to the complicated process of assessing reproductive toxicity data for drugs in development from numerous sources, with the end result being an understanding of potential drug-related signals. The IAM is designed for FDA reviewers who will likely not have reproductive toxicity as their primary expertise.

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Pharmaceutical Research and Manufacturers of America

It will however, be used by an even broader population within industry, both with and without a primary expertise in reproductive toxicity. Thus it is important that the IAM be as unambiguous as possible, so as to yield consistency across the industry and between industry and FDA. To this end, the critique of the Reprotoxicity Technical Group focuses on consistency and clarity of understanding of how to use the IAM. For example, we are seeking greater clarity around how to identify a signal and what exactly constitutes a signal.

The Technical Group strongly prefers that the end result of the IAM not be a numerical ranking, but a summary narrative of evaluation that leads to a summary risk statement in labeling.

The detailed comments of the Technical Group are outlined below. Please note that where we have suggested text, insertions are outlined and deletions are shown in strike-through font.

Lines 23-45: I. INTRODUCTION

Lines 34-36. The guidance states that this integration process does *not* consider the nature of the adverse response (e.g., severity, reversibility, or reparability). However, the IAM should consider the nature of adverse responses in the assessment of signal strength which is fundamentally important to any estimation of risk and to the purpose of the IAM.

Lines 46-160: II. BACKGROUND

Lines 73-76 (II B "Types of Reproductive and Developmental Toxicity Evaluated"). Male and female fertility should be evaluated as separate classes of reproductive toxicity. Lumping male and female fertility together results in a spectrum of effects which is too broad. Thus, there should be four classes of reproductive toxicity: (1) male fertility; (2) female fertility; (3) parturition; and (4) lactation.

Lines 117-120 (II B "Types of Reproductive and Developmental Toxicity Evaluated"; 1 "Reproductive Toxicities - Lactation"). The present wording of this section implies that the mere presence of drug in the milk constitutes an adverse effect. However all drugs may be excreted into milk in some amount, and the presence of drug in milk does not necessarily cause any adverse effect. Therefore the wording of this section is unclear concerning what would or would *not* constitute an effect on "lactation." The wording of this section should be clarified to state that the impairment of lactation is the actual adverse effect.

Lines 139-141 (II B "Types of Reproductive and Developmental Toxicity Evaluated"; 2 "Developmental Toxicities - Dymorphogenesis (Structural Alterations)"). It should be acknowledged that growth alterations as a class of developmental toxicity may in some cases appropriately include reductions in ossification (e.g. incomplete) depending upon the scope of overall developmental toxicity profile caused by the drug. For example, a reduction in ossification of peripheral structures such as phalanges, carpals, metacarpals, etc, when observed with a reduction in fetal weight, should be considered a concordant alteration of growth, rather than dymorphogenesis, when it occurs in the absence of other changes in the offspring.

Lines 145-149 (II B "Types of Reproductive and Developmental Toxicity Evaluated"; 2 "Developmental Toxicities - Alterations to Growth"). Anogenital distance is an endpoint that may in some cases represent dymorphogenesis (structural alteration) as opposed to an alteration of growth. While anogenital distance is assumed to be an index of growth when it positively correlates with offspring body weight, the gender-specific effects of some drugs (e.g. those causing hormonal changes) on anogenital distance in the absence of an effect on body weight would represent dymorphogenesis. This would clearly be the case when a change in anogenital distance occurs in conjunction with effects on urogenital sinus derivatives (e.g., hypospadias or altered accessory sex organ development).

Lines 161-806: III. DISCUSSION

Lines 234-239 (III A "Overall Decision Tree (Figure A)"; 3 "Presence or Absence of a Signal"). Before the question "Was there a positive signal (suggesting toxicity)?" can be answered, some general guidance or clarity concerning the minimum criteria for a positive signal is needed. Statistically significant differences alone should not necessarily constitute a positive signal, and therefore some general statements concerning other more compelling criteria would be useful. These criteria should include biological plausibility, reproducibility, drug- or species-specific mode of action, relationship to an animal-specific metabolite, and/or clear dose-response relationship.

Lines 308-316 (III B "No Signal (Figure B); 3 "Class Alert"). There is insufficient scientific knowledge to evaluate human risk based on chemical structures; therefore, class alerts should focus on compounds with related modes of action. Furthermore, similar modes of action of two different chemical entities would only suggest class alerts if the mode of action was determined to be related to the reproductive or developmental toxicity.

Lines 321-341 (III B "No Signal (Figure B); 4 "Signals for Related Types of Reproductive and Developmental Toxicity"). PhRMA suggests that this section is not necessary because all of the positive findings will be described in

the Summary Risk Conclusions and there is no need to state that other "related" signals were negative. Any uncertainty factors can be addressed in the Conclusion (see end of document).

Lines 347-377 (III C " One or More Positive Signals (Figure C)"; 1 "Overview of the Integrative Process"). If FDA accepts our suggestion that Male Fertility and Female Fertility should be distinct classes of reproductive toxicity, **line 376** should be revised as follows: "~~seven~~eight reproductive or developmental classes."

Lines 381-399 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"). Intra-species concordance manifested as related forms of toxicity is most likely to represent multiple findings within a single class of developmental toxicity. Thus, PhRMA recommends the following wording at **lines 382-385**:

"Multiple positive findings signals in a single related types class of reproductive or developmental toxicity within the same species indicates intra-species concordance of effects (e.g., a reduction in normal growth and an increase in developmental mortality). The observation of two or more positive signals for structural abnormalities in tissues of multiple embryonic origin (e.g., defects affecting soft tissue, skeletal tissue, and/or neural tissue) is an example of intraspecies concordance."

Further, and consistent with established interpretations of inter-species concordance, findings in multiple species ought to be within a single class of toxicity. Thus, PhRMA recommends the following wording at **lines 386-399**:

"Positive signals for the same or a related type class of toxicity (whether developmental or reproductive) across species indicates interspecies concordance. In general, findings for which there is intra- or interspecies concordance are more convincing than a positive signal in only one toxicity class in only a single species."

PhRMA recommends deleting the following text (**lines 391-399**) from this section of the Guidance, as it will be considered in the context of the Summary Risk Statement.

~~In evaluating potential human risk for adverse reproductive or developmental outcomes, if there is interspecies concordance for a single adverse effect it may be reasonable to conclude that a similar effect is the most likely adverse event to be seen in humans treated with the drug. If different but related adverse effects are seen in multiple test species (e.g., alterations to growth in one species and developmental mortality in another, or parturition effects in one species with lactation effects in the~~

~~second), it may be reasonable to assume there is some level of risk for categorically related endpoints in humans."~~

Lines 415-438 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance; a "Signal Strength, Part I - Cross-Species Concordance")

Because the term used elsewhere in the document is *inter-species concordance*, the title of this section should be "Inter-Species Concordance," not "Cross-Species Concordance."

PhRMA recommends the following wording:

"As indicated above, tThe defining characteristic of ~~cross~~inter-species concordance is a positive signal in the same class of reproductive or developmental toxicity in more than one species. ~~Cross~~Inter-species concordance is most likely to be identified for ~~structural abnormalities the developmental toxicity classes of (dysmorphogenesis), or developmental mortality, or alterations to growth,~~ because these toxicities are frequently detected in the *organogenesis* testing paradigm, in which multiple species are typically evaluated. In addition, alterations to male or female fertility, as assessed by endocrine dysfunction or gonadal histopathology (which may alter fertility) may be indirectly detected in subchronic and chronic toxicity studies in rodents and nonrodents. When ~~cross~~inter-species concordance is observed, there is increased concern for reproductive or developmental toxicity in humans. In contrast, there is decreased concern when a signal is detected in only one species (with the proviso that the negative species is an appropriate animal model and the studies were adequate in design, dosing, and implementation). Concern is unchanged if the toxicity class was evaluated in only one species. For alterations to parturition or lactation, it's often not possible to assess ~~cross~~inter-species concordance because peri- and postnatal studies to assess these classes of toxicity are usually done in only a single species."

Lines 442-459 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; a "Signal Strength, Part I - Multiplicity of Effects"). Multiplicity of effects as defined within a class would be addressed as intra-species concordance (see above). Thus, PhRMA recommends that the phrase "intra-species concordance" replace the current term "multiplicity of effects." Consistent with this approach, PhRMA recommends editing of lines 442-459 as follows:

~~"Multiplicity of effects refers to the observation, in a single species or animal model, of two or more positive signals within one of the two general categories of toxicity (reproductive or developmental) or within one of the seven classes of reproductive or developmental toxicities. The~~

~~observation of increased embryo-fetal death and structural abnormalities (dysmorphogenesis) in an animal test species is an example of multiple positive signals within a general category. The observation of two or more positive signals for structural abnormalities in tissues of multiple embryonic origin (e.g., defects affecting soft tissue, skeletal tissue, and/or neural tissue) is an example of multiple positive signals in a toxicity class. If all species examined demonstrate multiplicity of effects, there is increased concern for reproductive or developmental toxicity in humans. If there are positive signals in two or more species, but multiplicity of effects is observed in only one species, concern is unchanged for this element. If no species studied exhibits multiplicity of effects, there is decreased concern.~~

The presence of intra-species concordance would increase concern. Concern is unchanged if intra-species concordance is not present.

Lines 486-513 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; b "Signal Strength, Part II - Maternal Toxicity").

PhRMA recommends changes in this section for the following reasons:

1. In addition to the well-known consequences of maternal toxicity for fetal well-being, generalized toxicity may alter fertility, both in males and in females. For this reason, PhRMA suggests that the term "Parental Toxicity" be used.
2. The first sentence states that the magnitude of offspring effects versus the severity of maternal toxicity should be considered. However, the subsequent discussion is all about dose, not severity of effect. Thus, PhRMA recommends that references to paternal and developmental NOEL replace current references to effects (paternal or developmental).

PhRMA recommends that the section "Maternal Toxicity" be reworded as follows:

"ParentalMaternal Toxicity

~~In weighing a signal of toxicity, the magnitude of adverse effects~~no effect level in the offspring versus the ~~severity of~~no effect level for maternal (and, for fertility studies, paternal) toxicity should be considered when drawing a conclusion about the relevance of the F₀ toxicity to ~~effects observed in the offspring~~the positive signal. This assessment is relevant to all eight~~seven~~ classes of reproductive and developmental toxicity. A positive signal for reproductive or developmental toxicity occurring at doses that are ~~not maternally toxic~~in the absence of significant parental toxicity increases concern for human reproductive or developmental toxicity. There is

diminished concern iff a positive signal is observed only in the presence of frank ~~maternal-parental~~ parental toxicity, there is decreased concern, provided that ~~the positive signal may~~ can be reasonably attributed to ~~parental~~ maternal toxicity. Concern is unchanged if there is a positive signal only in the presence of parental toxicity, but the relationship between parental toxicity and the signal is unclear.

When evaluating a positive signal in two or more species, assessment of the implications of ~~maternal or paternal~~ parental toxicity should be based on a composite analysis of the data from all adequately studied species. If a positive signal is seen in two or more species in the absence of significant ~~maternal-parental~~ toxicity, there is increased concern for adverse human reproductive outcomes. If a positive signal is seen only in the presence of clear relevant ~~maternal-parental~~ toxicity in multiple species, there is decreased concern. If there is nonconcordance between test species as to the presence and relevance of ~~maternal-parental~~ toxicity, there may be no change in the overall level of concern for this contributory element.

If any species is considered inappropriate to assessing the implications of ~~maternal or paternal~~ parental toxicity, the evaluation should be performed using the remaining available data."

Lines 517-524 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; b "Signal Strength, Part II - Dose-Response Relationship"). PhRMA recommends the following wording:

"Dose-Response Relationship

Concern for human reproductive or developmental toxicity is increased when a positive signal is characterized by any of the following: (1) increased severity of adverse effects with an increase in dose, (2) increased incidence of adverse effects with an increase in dose, or (3) a high incidence of adverse effects across all dosed groups. The presence of adverse events at the high dose alone would cause concern to be unchanged. Conversely, the absence of ~~all three~~ any of these indicia patterns of dose-response would be cause for ~~unchanged or~~ decreased concern. The extent of the increased severity and incidence of adverse effects is also an indicator of the level of concern. There is increased concern if the incidence is high or the effect is severe; and decreased concern if the incidence is low or the effect is mild. Intermediate incidences and severity would be cause for an unchanged level of concern.

Lines 536-546 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; b "Signal Strength, Part II - Rare Events"). The occurrence of treatment-associated findings that occur rarely in the background population is a cogent reason to make the determination of a positive signal. As such, we recommend that this section be deleted.

NEW CONTRIBUTING ELEMENT to Signal Strength, Part II proposed by PhRMA. There needs to be some consideration of the potential biological impact of the signal when predicting risk to humans. Therefore, PhRMA proposes the addition of the following as a contributing element to Signal Strength, Part II:

"Impact

Concern for human reproductive or developmental toxicity is increased when the signal would be expected to seriously affect viability or function (e.g., a life-threatening malformation). When the signal would not be expected to adversely affect viability or function (e.g., slight effect on fetal body weight or increased skeletal variations), it would be cause for decreased concern."

Lines 550-612 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; c "Pharmacodynamics"). In this section, PhRMA suggests a change in the term "therapeutic index" to eliminate confusion between the use of the term in this tool and the conventional application of this term. We suggest the term *therapeutic comparison* [TC].

We also urge FDA to make the modifications listed below for lines 557-612.

Lines 557-587 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; c "Pharmacodynamics - Therapeutic Index (TI)").

Lines 557-562. We suggest that these lines be modified as follows, for clarity: "The ~~HTC~~ is used to identify the extent to which there is overlap between test species therapeutic conditions and toxic conditions ~~doses and doses~~ that cause reproductive or developmental toxicity. For whatever values are employed in the comparison, the unit of measure must be the same for each. This evaluation is best performed using ~~It is unusual to obtain well-defined dose-response curves~~ for toxicity and efficacy from a single species. When such data are not available, ~~Thus,~~ the use of estimations or surrogate endpoints (related to the therapeutic mode of action/mechanism) for this evaluation may be warranted."

Line 565 (Footnote 7). It is generally very difficult to obtain the values for TD₁₀ and ED₉₀ in the same species and from comparable in vivo studies. We suggest an alternative ratio built from the lowest does causing a toxicity signal LOEL in the numerator and the pharmacologically effective dose in the denominator.

Both values are normally and easily available from existing pre-clinical studies. We suggest replacing the wording for footnote (7) with the following, to clarify the terms used to derive the ratio for the TC:

“Comparisons should be made for the same species from in vivo studies wherever possible. The units of measure used in the construction of the ratio should be the same for the numerator and the denominator. The LOEL (as dose or concentration) should be defined by an appropriate exposure metric (C_{max} , AUC, etc) that produced the lowest observed effect level for the toxic reproductive or developmental response. The pharmacologically effective dose (as dose or concentration) should be defined by the same exposure metric (the C_{max} or other appropriate exposure metric). These parameters can be estimated. In some instances estimation of the pharmacologically effective dose can be based on in vitro cell inhibition studies (frequently seen for antibiotics and antineoplastic agents). When available, scientific justification for the drug exposure metrics used for comparison should be provided. When data are not available, no ratio should be evaluated unless use of a cross-species comparison can be justified.”

Lines 567-573. FDA suggests that for determination of the levels of concern the ratio values of 5 – 20 be used. A rationale for the selection of these values is needed and could be provided as a footnote.

Line 583. PhRMA suggests that “observed” be replaced with “being evaluated.”

Lines 591-598 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; c "Pharmacodynamics - Biomarkers as a Benchmark").

Line 593. Biomarkers can be important tools for the determination of risk and for the purpose of this tool it is necessary to make clear that the biomarker being used must have relevance to the reproductive or developmental toxicity under evaluation. PhRMA suggests the addition of the following sentence after "toxicity" on this line: The biomarker must be relevant to and serve as an indicator of the reproductive/developmental toxicity that has induced the positive signal under evaluation.”

Lines 600-612 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; c "Pharmacodynamics - Similarity between Pharmacologic and Reproductive Developmental Toxicologic Mechanisms”).

Lines 601 and 604. We suggest that there be a change in the wording of the heading on line 601, from "Mechanisms" to *Modes of Action*, as this is more relevant to information at hand when conducting the integrated assessment.

Similarly, the term *mode of action* should be substituted for the word "effect" on line 604.

Line 609. A definition of unchanged concern should be added to this section. We suggest insertion of the following sentence after "humans": "If the relationship of a potential mode of action causing the positive signal to the intended pharmacological mode of action of the drug is unknown, the level of concern is unchanged."

Lines 609-612. Any signal that can be attributed to an animal-specific pharmacological response would be considered in the initial signal identification process and would have contributed to a conclusion of "no signal" for this particular event. As such the sentence at lines 609-612 can be omitted ("~~There is less concern if the positive signal is attributed to an animal-specific pharmacological response, even though it may be an extension of the pharmacologic effect of the drug (e.g., pregnancy loss in rats due to hypo-prolactinemia)~~"). Alternatively, the sentence should be amended to reference the earlier consideration of the signal. For example, the following wording could be substituted: "An animal-specific pharmacological response, even though it may be an extension of the pharmacologic effect of the drug (e.g., pregnancy loss in rats due to hypo-prolactinemia) would be factored in the initial evaluation of signal identification."

Line 622-657 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; d "Concordance between the Test Species and Humans"). Unless there is a known or plausible causal relationship between a signal and metabolic/drug distribution profiles or general toxicity profiles or biomarker profiles, simply having concordance between test species and humans should not raise the level of concern. If no relationship can be found, then the concern should be unchanged.

If the ADME parameters that were relevant for the observed toxicity are not present in humans, then the toxicity observed in the test species should not be counted as a positive signal and should not be assessed using the IAM.

We urge FDA to make the modifications listed below for lines 623-657.

Line 623-633 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; d "Concordance between the Test Species and Humans - Metabolic and Drug Distribution Profiles"). We suggest that the following be added at the end of **line 623**: "The test species are usually chosen because they have similar distribution, elimination or biotransformation profile to humans."

Further, we would modify **lines 627-633** as follows: "If there is a known or plausible causal relationship between the ADME similarity and the reproductive

or developmental toxicity signal, then reproductive and developmental toxicities induced by compounds whose metabolic and distribution profiles are very similar in animals and humans increases concern for reproductive or developmental toxicity in humans. On the other hand, if there is no known relationship between an ADME finding and the mode of toxicity or the toxicity observed, then the level of concern is unchanged even if there is ADME similarity between animals and humans. For compounds with highly dissimilar metabolic and disposition profiles between animals and humans, any toxic effect seen in the test species that is attributable to a dissimilar ADME parameter is not considered as a signal and need not be assessed using this tool."

Lines 644-647 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; d "Concordance between the Test Species and Humans - General Toxicity Profiles"). PhRMA suggests that these lines be modified as follows: "General toxicity should only be considered if there is a known biological relationship between a signal of general toxicity seen in adult animals and the reproductive or developmental toxicity observed (e.g., shared mode of toxicity). Once this relationship is established, if the overall toxicity profile of a drug in one or more test species with a positive signal is similar to that in humans, there is increased concern for reproductive or developmental toxicity in humans. If the overall toxicity profiles are dissimilar, there may be decreased concern for reproductive or developmental toxicity in humans when the correlating signal of general toxicity has not been observed in humans tested at adequate exposures. If the relevance of general toxicity to reproductive or developmental toxicity is not established, then the concern is unchanged. When"

Line 657 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; d "Concordance between the Test Species and Humans - Biomarker Profiles"). PhRMA would add to the end of this line: "That is, relevance of the biomarker to reproductive or developmental toxicity needs to be established in order for the level of concern to be affected. In some instances, general toxicity may be considered as a biomarker of reproductive or developmental effect."

Lines 669-700 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; e "Relative Exposures - Kinetic Comparison of Relative Exposure"). The proposed concern level score for relative exposure is based on the ratio of the NOEL for a class of reproductive or developmental toxicity and the maximum recommended clinical dose. Ratios of ≤ 10 , >10 to <25 , and ≥ 25 are proposed to establish concern scores. The most appropriate endpoint of relative exposure (AUC, C_{max} , C_{min} , BSA, etc..) should be used for the ratio calculations.

These ratios as referenced in the draft document appear subjective because the basis and/or rationale for these cutoffs are not provided. Because this document

is meant to be a training tool and guide for FDA reviewers and to provide a common basis of understanding between the agency and sponsors, we recommend that the FDA provide a textual discussion of the basis/rationale for the ratio cutoffs. This information can be provided in a footnote.

The FDA has previously provided a rationale for the ratio cutoffs based on the known intraspecies variation (10x) in internal exposure (blood AUC) following administration of a specific dose of drug.¹ Given this level of internal exposure variability, a NOEL maximum clinical dose ratio of >25 should preclude overlap in exposure (AUC) between the safe level in animals and the therapeutic level in humans. Conversely, a ratio of <10 would result in some expected overlap in exposure, with patients' exposures potentially exceeding NOELs from the animal model. Although this approach may work when exposure is expressed as AUC, the approach may not hold for other measures of exposure (C_{max} , C_{min} , etc.) that may be important in assessing toxicity/safety.

Lines 704-727 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; e "Relative Exposures - Biomarkers as a Measure of Relative Exposure").

Biomarkers as a measure of relative exposure use a concept of exposure ratios (test species NOEL/maximum therapeutic exposure) similar to that of the kinetic comparison of relative exposure, with the exception that the biomarker ratio is normalized to biomarker response. As requested for the kinetic comparison of relative exposure, PhRMA recommends that the rationale/basis for the biomarker approach be added to the draft document. The rationale for the ratio cutoff with the use of biomarkers is of particular importance as the intraspecies variability argument is not as apparent when calculations are based on the "ratio of a ratio." To improve the understanding and application of biomarkers in the measure of relative exposure, a sample calculation demonstrating the ratio of a ratio concept should be added to the document, such as:

Example: Ratio A = signal NOEL / animal biomarker LOEL
 Ratio B = human dose / human biomarker LOEL
 If Ratio A / Ratio B < 10 then increased concern
 If Ratio A / Ratio B ≥ 10 then decreased concern

The text should also acknowledge that biomarkers are typically not available for most forms of reproductive and developmental toxicity. Furthermore, in situations where test species biomarkers are available, human biomarker data

¹ This rationale was provided by FDA at a workshop entitled "Integrated Reproductive Risk Guidance" which was cosponsored by the Drug Information Association (DIA) and FDA, and held in Washington DC at the Washington Marriott Hotel on Jan 22, 2002.

will not be generated if it requires increasing doses well beyond the maximum therapeutic exposure. Finally, the text should explicitly note that the biomarker must be relevant to and serve as an indicator of the reproductive/ developmental toxicity that has induced the positive signal under evaluation.

Lines 731-742 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; f " Class Alerts"). The science is not developed enough for evaluating human risk based on knowledge of similar chemical structures. The class alert section should focus on a compound's mode of action rather than chemical structure.

PhRMA suggests that the text in this section be replaced with the following wording:

"Given another drug with the same mode of action, exhibiting the same class of reproductive or developmental toxicity in animals and having known human outcomes, there will be increased concern if the comparator drug is known to produce reproductive or developmental toxicity in humans, and decreased concern if comparator drug is known not to produce reproductive or developmental toxicity in humans; otherwise this contributing element is not applicable."

Lines 761-805 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; g "Summary/Integration of Positive Findings"). Changes may be required to reflect PhRMA's suggestion that there be eight reproductive or developmental toxicity classes.

Lines 776-786 (III C " One or More Positive Signals (Figure C)"; 2 "A Note on Intra- and Inter-Species Concordance"; g "Summary/Integration of Positive Findings"; 3). PhRMA is concerned that the proposed "summary risk conclusions" will not be helpful to patients and health care providers because individuals can vary widely in how they make a distinction, or lack of distinction, between "predicted to increase risk" and "may increase risk." In particular, the phrase "May Increase Risk" could result in both overly conservative reactions as well as a failure to identify drugs with substantial risks, and the use of this phrase for an overall conclusion is not recommended. Furthermore, the definitions (**lines 792-805**) are solely within the context of "when used in accordance with dosing information in the product label" which can be both an ambiguous context (drugs with wide-ranging dosages) and a restricted context (seemingly disallows risk characterizations for overdose).

Although risk assessment based on nonclinical information has uncertainties, PhRMA believes it is possible to make a clear statement of risk given the extent of data under consideration by the six factors. For example,

{a} "Animal studies do not predict an increased risk of _____ above background occurrence in the general population under conditions of _____." Then go on to describe the contributing elements most relevant to this prediction, plus any uncertainties.

-or-

{b} "Animal studies do predict an increased risk of _____ above background occurrence in the general population under conditions of _____." Then go on to describe the contributing elements most relevant to this prediction, plus any uncertainties.

PhRMA suggests this approach for the following reasons:

1. It eliminates ambiguity in the statement of risk while providing opportunity to openly indicate areas of uncertainty.
2. It provides greater flexibility in the identification of the risk (can be more specific than, for example, "Dysmorphogenesis").
3. It provides explicit statement of the exposure conditions.

Moreover, rather than to strictly define net values demarcating {a} or {b}, we suggest that the choice be based on the weight of evidence using scientific judgment and available human data along with the net value. Although there can be general guidance on the use of the net value, it should not absolutely dictate conclusion {a} or {b}. This would allow for integration between nonclinical and clinical data, particularly registries of drug use in pregnancy. The goal should be the most appropriate summary risk conclusion for each case, and this requires some flexibility in judgment at the end of the process.

Below, we have provided four examples of Summary Risk Conclusions (Note: if there are known adverse pregnancy outcomes in humans that information takes precedence):

PhRMA Examples of Summary Risk Conclusions with No Positive Signal

Animal studies do not predict an increased risk of adverse pregnancy outcome above background under conditions of drug exposure exceeding the maximum clinical dosage. Animal studies are not always predictive of humans, and adequate human data on use in pregnancy are not available for this drug or drugs with the same mode of action.

Animal studies do not predict an increased risk of adverse pregnancy outcome above background under conditions of drug exposure exceeding the maximum clinical dosage. A survey of over 200 human pregnancies with drug exposure has not identified a risk of adverse pregnancy outcomes.

PhRMA Examples of Summary Risk Conclusions with a Positive Signal

Animal studies do not predict an increased risk of adverse pregnancy outcome above background under conditions of drug exposure within the range of recommended clinical dosage. At exposure (AUC) levels 7-times that associated with the maximum clinical dosage, there was maternal toxicity and fetal growth retardation in rats, evidenced by reduced (10%) fetal body weight with no concordant findings in this species or in rabbits. This finding occurred when rats were treated throughout organogenesis at 5-fold the pharmacologically effective dose in rats and is not thought to be related to the intended drug action. Animal studies are not always predictive of humans, and adequate human data on use in pregnancy are not available for this drug or drugs with the same mode of action.

Animal studies do predict an increased risk of fetal malformation under conditions of drug exposure associated with therapeutic activity and lowering of serum Z levels. There were ocular and brain defects in rats and in rabbits treated during organogenesis at doses (not maternally toxic) equivalent to the pharmacologically effective dose in animal models. The malformations were dose-related in severity and incidence and were thought to be a result of the drug's intended antagonism of the X receptor. Animal studies are not always predictive of humans, and adequate human data on use in pregnancy are not available for this drug or drugs with the same mode of action.

PhRMA is pleased to submit these comments to the FDA. If you require further information, please do not hesitate to contact me.

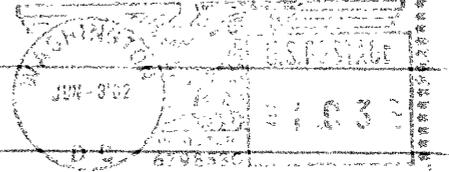
Sincerely,

A handwritten signature in black ink that reads "Sara Radcliffe". The signature is written in a cursive, flowing style.

Sara Radcliffe

PRMA

Sara Radcliffe



Robert Osterberg, Ph.D.
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