

Comments on Draft Guidance: Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities

General Comments

- Comment 1

At a recent DIA/FDA conference held 22 January 02 in Washington, D.C., Dr. DeGeorge and other FDA leaders were asked: “Do you anticipate changes in preparation of repro-tox study reports and summary documentation as a result of implementation of this Guidance?” Answer: “Yes, and some sponsors are already incorporating the concepts contained in the Draft Guidance for Reviewers in current submissions to FDA.”

Thus, while Draft Guidance is directed at FDA Reviewers, it has much the same impact on Industry as a new FDA Guidance to Industry, and can not but impact communication of reproductive toxicology findings in study reports, summary documentation, Investigator Brochures, etc. Perhaps the final document should be redirected and issued as a Guidance to Industry?

- Comment 2

There are three classes of outputs described in the Guidance:

1. Text to be reflected in product labeling (lines 200-203, 220-223)
2. Text to be reflected in the evaluation(?) (lines 298-301, 335-341)
3. Summary risk conclusions (lines 776-806)

The first is straightforward, although there is apparent confusion concerning another DRAFT Guidance to Industry (see below) that will address product labeling. The evaluation described in the second should be defined. Will Sponsors receive this evaluation? The fate of the summary risk conclusions is also not defined. Will these be carried forth into product labeling, into the evaluation, both, or neither?

AZ recommends that additional clarification and definition of the three types of outputs identified in the Guidance be provided.

- Comment 3

A separate DRAFT Guidance for Industry (not yet available) is in preparation which will link the net score ranges (see above) to specific language that will be required in future US product labeling (probably replacing the current Category A to X labeling (DeGeorge, J., DIA/FDA Conference, Washington, DC, 22 January 02). However, examples of product labeling are included in this Guidance (lines 200-203, 220-223). What will be the linkage between the recommended statements in this Guidance and those in the future Guidance? Would it not be better to review both DRAFTs together for consistency?

Because of the critical linkage between the these two documents AstraZeneca recommends that final issue Guidance for Reviewers document be delayed until it can be reviewed with the proposed (but not yet available) Guidance for Industry document.

- Comment 4

At the recent DIA/FDA workshop held 22 January 2002 in Washington, D.C., approximately 80 participants were divided into three working groups to evaluate three separate case studies using the tools outlined in the Guidance for Reviewers. In general, the results of those three case studies were as follows:

- There was a high degree of agreement within the working groups as to the overall score for a specific data set.
- There was a high degree of concordance between groups as to values assessed for individual factors for a specific signal within a specific case study – the greatest variation was usually within the assessments of the Signal Strength factors (I and II). Variation in scoring was often related to different interpretations of specific text within the Guidance.
- Overall, all participants felt that the assessment of potential risk to humans arrived at using the tool (Figure C) was more severe than had the participants used the more intuitive “weight of evidence” schemes used by knowledgeable toxicologists. When questioned, Dr. DeGeorge insisted that the present Case studies had been biased towards compounds having clear signals and that based upon the work of “other test groups” using data sets that did not include signals – it was his experience that no bias towards more severe ratings had occurred. Dr. DeGeorge encouraged the participants to take the tools “home” and to try them out on additional internal datasets.

AstraZeneca recommends that, in accord with Dr. DeGeorge’s recommendations at the meeting, final issue of the Guidance for Reviewers be delayed until additional testing like that performed at the DIA/FDA conference is conducted upon genuine data sets and the results published/presented so that the impact of the Guidance can be more fully assessed and described.

Dr. DeGeorge’s position notwithstanding, it is AstraZeneca’s assessment that the tool (Figure C) could be biased toward more conservative interpretations of potential risk to humans because using the six-step approach it is difficult to foresee specific findings (or lack of findings) that would actually reduce the Reviewers overall level of concern (a value of –1), as opposed to not changing that level of concern (a value of 0). While AZ has no a priori objection to more conservative interpretations, without knowing the content of the proposed (but not yet available) Guidance to Industry that will link those interpretations to specific language to be included in product labels, it is not currently possible to evaluate the impact of the proposed tool (Figure C).

AstraZeneca urges that finalization of the Guidance to Reviewers be delayed and linked with finalization of the (as yet unavailable) DRAFT Guidance to Industry.

- Overall Comments: Since both the inevitable effect and the intent of the guidance (as noted by FDA at the 22 January 02 meeting) is to change the way that Industry conducts and reports reproductive/developmental toxicology studies, we strongly believe that FDA/Industry relations are better served by progressing this directly as a Guidance to Industry rather than trying to effect these changes indirectly through the proposed Reviewer Guidance.

Specific Comments

Section, Page Number, Line Number	Comment
<p>Section III.A.2 (lines 210-230)</p> <p>Section III.B.2 (lines 287-305)</p>	<p>The term “relevant” is used. Routinely, the rat has been employed in DART studies, along with the rabbit in developmental studies. Thus, one assumes that such models are relevant. However, since DART studies are generally completed or ongoing before ADME/PK data in humans are available, the questions in Section III.B.2 (lines 287-305) can only be answered following performance of human clinical trials. If the answer to one or more of the questions is no, then the conclusion is that the study(ies) may not be adequate. Clarification is needed whether and when the “No” answer results in the Sponsor: a) performing more tests in order to obtain evidence that the studies are “adequate,” b) accepting specific language/categorization in the final product label, or c) both.</p>
<p>lines 470-471</p> <p>lines 537-538</p>	<p>The use of the phrase “rare events” is a major flaw in this guidance. On the one hand, the guidance states (lines 470-471): “If the positive signal occurs only during processes that are of limited relevance to humans (rare), there would be less concern for adverse human reproductive outcomes.” Later on (lines 537-538) it states: “Thus, an increased frequency of positive signals for rare events in drug-exposed animals increases concern for reproductive or developmental toxicity in humans.” These two statements are incompatible as written. The guidance does not specify whether one specific rare event is involved or whether two or more rare events constitute a problem. In any study, one can expect to identify a multitude of events, especially minor skeletal anomalies (variations) at the MTD. Such anomalies are likely to occur infrequently in the control group. Thus, the frequency in one’s historical control may be low, leading one to conclude that they are rare events. Clarification of what is meant by “rare” is needed.</p>

Section, Page Number, Line Number	Comment
lines 555-587	<p>The use of the TI10/90 ratio (lines 555-587) appears arbitrary and of questionable value in assigning a signal. The TI10/90 for an oncology drug will often be low and handled differently than therapeutics for other indications. Also, it will often be the case that different species will be used to assess efficacy than those used to assess toxicity. In DART studies, treatment is usually given over relatively long periods (e.g., organogenesis or fetal period to weaning or preweaning to implantation), thereby often resulting in a lower MTD than if the drug was given over shorter periods, while, clinically, the therapeutic often is given for shorter periods (e.g., the MTD in an acute study is often higher than in a chronic study).</p>
lines 669-700	<p>Although the relative exposures ratio (lines 669-700) also employs a relevant metric, in order to show decreased concern a ratio ≥ 25 must be obtained. This may be difficult to achieve especially considering the low levels likely to be obtained in a DART study at the NOAEL. Thus, both the TI and relative exposure ratios are more likely to result in values indicating increased concern, making it unlikely that the decreased concern designation would be assigned (see overall comments above).</p>
	<p>Route of administration may be particularly problematic for Reviewers judging the adequacy of reproductive toxicology study designs. For example: Proton pump inhibitors (PPIs) are generally administered orally in humans. In developmental toxicology studies (segment II) in rabbits, PPIs administered orally are associated with unacceptable maternal toxicity at relatively low doses, limiting systemic exposure to levels at or even below human therapeutic exposures. However, PPIs given intravenously to rabbits achieve significantly higher systemic exposure before unacceptable maternal toxicity is apparent. Other non-therapeutic routes of administration (subcutaneous, intramuscular, etc) may also be associated with higher systemic exposures at the maximum tolerated dose (MTD) than the intended therapeutic route. On the other hand, specific routes of administration may or may not be associated with the same metabolite profiles as the intended therapeutic route.</p> <p>The Guidance to Reviewers should clarify how Reviewers assign priority: Should priority be given to higher systemic exposure or to therapeutic route, or some combination of the two?</p>

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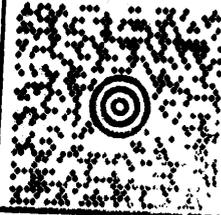


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