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Director
Scientific and Regulatory Affairs



August 3, 2005

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

Re: Request for Comments on the Draft Guidance for Industry on Safety Testing of Drug Metabolites [Docket No. 2005D-0203, Federal Register, Vol. 70, No. 107, June 6, 2005]

Dear Ms. Aisar Atrakchi:

The attached comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA is a voluntary, non-profit trade association representing the firms that discover, develop and produce prescription drugs and biologic products. The large majority of new prescription medicines approved for marketing in the United States are produced by PhRMA member firms.

A PhRMA Joint Committee team has carefully reviewed the draft guidance and would like to take this opportunity to provide comments, which are attached.

Your consideration of these comments is appreciated. Please contact me if you have any questions.

Sincerely,

A handwritten signature in cursive script that reads 'Michael Garvin'.

Michael Garvin, Pharm.D.

2005D-0203

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Pharmaceutical Research and Manufacturers of America

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PhRMA Committee Comments on draft “Guidance for Industry: Safety Testing of Drug Metabolites,” released on June 3, 2005 (Docket No. 2005D-0203)

General Comments

We appreciate the Agency’s efforts in providing recommendations on the safety assessment of unique human drug metabolites. We agree that it is important to understand the metabolism of new drugs as early as possible in development. However, the essential question that remains is how extensively do metabolites need to be identified and at what stage of the clinical development should this occur. We believe this question should be resolved on a case-by-case basis by extensive scientific discussions between the sponsor and the Agency. Because of the potentially profound effect on the speed and cost of drug development, we believe that there is a need for a continued discussion among experts and the Agency before this guidance is finalized. The goal of this discussion should be to achieve a consensus on the broad topic of safety testing of drug metabolites, including agreement on the definition of a major metabolite, situations in which metabolites need to be completely identified and tested, and the impact on drug development. One major issue requiring a careful re-examination is the designation of the arbitrary 10% threshold for major metabolites. The current draft guidance is useful as a concept paper to stimulate such discussion but there are significant complex issues that should be resolved before establishing Agency policy in this area. Further discussion among experts is needed before establishing rigid, rules-based recommendations for safety testing of drug metabolites. In effect, a collaborative effort should exist between a sponsor and the Agency in defining the most appropriate testing strategy to characterize the safety profile of unique human metabolites and major metabolites of a specific drug. Presently, only the last paragraph of the guidance allows consideration of testing on a case-by-case basis, but this exception is reserved for “drugs for serious or life-threatening diseases that lack an approved effective therapy.” We maintain that each drug development program with potential clinical benefit should qualify for similar flexibility.

Clarification of Language and Assumptions

- The definition of ‘dose’ used for decision-making is not clear (Appendix A: Decision tree flow diagram). Moreover, the definitions used in the document for decision-making relative to metabolite safety testing vary in different sections (cf Sections I, II, III.B, and Glossary). Much of the ambiguity arises from mixing two fundamentally different concepts. ICH S3A clearly indicates that the appropriate metric for quantification of systemic exposure is plasma concentrations or AUC of the parent compound and/or metabolites (Sections 3.2 and 3.8). In addition, Footnote 9 of Section 3.8 indicates that measurement of human metabolite concentrations in plasma of non-clinical toxicity studies is important to demonstrate adequate testing of metabolites. However, the draft Guidance confuses systemic exposure, as defined in ICH S3A, with non-circulating metabolites excreted in bile, feces, or urine and treats them equivalently. Subsequently, the guidance indicates that if Phase II metabolites

are detected in excreta, it can be assumed that systemic exposure has occurred. The text concludes that systemic exposure to metabolites in plasma and/or excreta are equivalent for determining adequacy of human exposure in nonclinical species. This interpretation differs significantly from international consensus guidelines. Excretory metabolites may represent a measure of exposure for the excretory organ but they may or may not represent a measure of systemic exposure. The measurement of excretory metabolites has value as qualitative data to demonstrate that a metabolic pathway exists in nonclinical species. The text on the measurement of excretory metabolites should be moved into a separate section devoted to supporting information and these metabolites should not be used as a quantitative measure of systemic exposure.

- The definition of 'threshold of concern' for metabolites is problematic. Although the use of systemic exposure (defined as AUC) is the international standard for defining safety margins for drugs, the definition of a threshold of concern for metabolites based upon the percentage of drug-related material in plasma also has value. This is the most direct means of evaluating human disposition in studies with a radiolabeled drug. For technical reasons related to the quantitation of metabolites by radiometric methods and the limitation of the amount of radioactivity that can be dosed to humans (maximum of ~100 μ Ci), it is difficult to reliably quantify minor metabolites comprising $\leq 10\%$ of total drug-related AUC. Thus, a 10% threshold of concern for drug metabolites is not reasonable based on unreliability of quantitation and the low likelihood that a metabolite at such levels could represent a substantive toxicological risk. Further, we believe the scientific process should not be bound by a simple quantitative % of circulating metabolites as the trigger point. Alternatively, we suggest that the relative ratio of animal-to-human exposure of metabolites (based on AUC) should define adequacy of coverage by nonclinical species and decisions to perform subsequent nonclinical metabolite testing would be data-driven and made on a case-by-case basis.
- The four examples cited in Section II of the draft Guidance to support the use of 10% threshold of drug related material in plasma are not appropriate and should be removed from the text. These examples involve the formation of chemically reactive metabolites that bind covalently to proteins and form conjugates that are excreted. In the case of the cyclophosphamide prodrug, metabolism leads to phosphoramidate mustard which alkylates DNA and thus provides the basis for the cytotoxic effects of this chemotherapeutic agent. In the case of the other drugs mentioned (halothane, felbamate, and acetaminophen), years of research were required to identify the reactive metabolites responsible for their toxic effects. More importantly, none of the reactive metabolites of these three drugs are detectable, *at any level*, in the plasma of nonclinical species or humans. More appropriate examples that involve significant systemic human plasma exposure to circulating toxic metabolites without adequate coverage of plasma exposure in nonclinical species should be provided, if they are available, to justify the recommendations of this draft Guidance.
- The proposed toxicology testing of synthetic metabolites raises a number of concerns from a scientific standpoint. The results of toxicity testing employing such a study

design may be misleading, and fail to characterize the true toxicological contribution of the metabolite when formed from the parent. Hence, the results of toxicity testing with a preformed metabolite, regardless of route of administration, need to be interpreted with great caution.

- We recommend rewording the sentence on lines 40-43 as follows: "During the past decade, the availability of new technologies enabled us to identify, to measure and to characterize metabolites that may have not been detectable by less sensitive methods. Such metabolites can now be routinely evaluated in cross-species safety assessments, which give us a better understanding of their specific contribution to the overall toxicological potential of the parent drug."
- We commend the Agency's interest to encourage submission of structure activity relationship analyses. We recommend additional guidance text clarifying that a chemical structure-based analysis should not be based only on the use of commercially available computational systems, but can incorporate expert examination and scientific literature-based support. We also submit that in certain cases a structure activity relationship risk analysis could be sufficient to "qualify" a suspect metabolite without additional hazard testing.

Impact on Development Timelines

- As noted in the Critical Path white paper, currently there is only an 8% chance of a drug candidate in phase 1 clinical trials ultimately reaching the market. The draft Guidance would effectively require that resource-intensive human ADME studies be conducted at approximately the same time as the phase 1 clinical trials in order to comply with the request for submission of final study reports on toxicity of a human metabolite prior to the initiation of phase 3 trials. Although the draft Guidance indicates that *in vitro* studies may be used for interspecies metabolism comparisons, these data would only give a qualitative comparison of metabolite profiles which would be insufficient to meet the quantitative in vivo criteria from human ADME studies that would serve as the definitive basis for metabolite synthesis and testing. This disconnect could be obviated by eliminating the recommendation that metabolite testing programs must be completed prior to the initiation of phase 3 clinical trials and indicating that any required testing should be completed prior to filing an NDA. Furthermore, in the rare circumstance that an unmonitorable, off-target toxicity that may be unique to a tested metabolite is discovered in a nonclinical study, timely IND safety reporting would mitigate the potential of exposing a large human population on study drug. Such a strategy is presently endorsed by the Agency in the timing of the standard two-year oncogenicity studies, whereby final reports are expected at the time of registration but not normally prior to phase 3.
- The text in lines 148-152 suggests that the majority of drug development programs are subject to nonclinical safety testing of metabolites. Generally, *all* adverse effects observed in nonclinical studies are assumed to have potential clinical relevance. In addition, a fundamental principle used for dose selection in nonclinical testing is that the top dose should be based on dose-limiting toxicity. This consideration, combined with the draft Guidance recommendation, will result in the need to test multiple

nonclinical metabolites regardless of true clinical relevance. The determination of whether an adverse effect is caused by the parent compound or a metabolite can take years of research and would significantly delay each nonclinical testing program that demonstrated dose-limiting toxicity. To prevent a significant increase in the amount of time required to develop new drugs, this text and recommendation should be removed. To the extent that such testing would advance a development program, it should be the sponsor's responsibility to consider the value of including such an assessment.

- The requirement for the synthesis and toxicology testing of metabolites represents a very significant resource commitment. The need to synthesize and test one or more metabolites will introduce a costly barrier to the development of a drug candidate and may prevent or delay the introduction of new therapies for unmet medical needs. The requirement that each *in vivo* metabolite safety testing program should be conducted with a high dose exhibiting dose limiting toxicity or a maximum feasible dose of 2000 mg/kg/day (Section IV.A.) means that large amounts of each metabolite would have to be synthesized for each testing program. The synthesis of each metabolite may require a synthetic procedure that differs significantly from that of the parent compound. If testing is required, a requirement for animal exposure to the metabolite that approximates human clinical exposure would be a more practical requirement.

Study Design Considerations

- If testing of drug metabolites is required, general toxicity tests ranging from 14-90 days should be sufficient, along with genetic toxicity testing and a safety pharmacology evaluation to assess the potential for QT prolongation, as appropriate. Longer term testing will require large amounts of the synthesized metabolite and will unduly delay drug development without a commensurate increase in the value of the safety assessment program. There is published literature demonstrating that limited additional findings of toxicological significance are detected in study durations beyond 90 days. Due to the nature of these metabolites, (e.g., highly reactive, toxic, short or long half-life, etc.) we believe that each testing strategy should be created following discussions between the sponsor and the Agency. We recommend that sponsors should be able to discuss with the Agency the most appropriate testing strategy for the assessment of these metabolites on a case-by-case basis.
- The guidance should specifically state that the safety of a drug metabolite is considered to be adequately investigated when there are quantitative profile similarities or plasma exposure margins in at least one of the two required preclinical species (rodent or non-rodent). If metabolite safety testing by administration of a synthesized metabolite is warranted, the final Guidance should also clarify whether safety testing of a synthesized metabolite in a single species provides adequate investigation of clinically relevant toxicity. The guidance should also define the dosing strategy to be used (i.e., to an MTD or to an adequate multiple of human exposure, where "adequate" needs to be defined). This could have significant implications on compound requirements.
- Regarding the general considerations for study design (lines 210-215) we recommend changes in the wording as follows: 1) "eliciting exaggerated

pharmacological effect” to “eliciting augmented pharmacological effect”; 2) “*activating receptors different from the parent drug target receptors*” should read “activating different receptors from the parent drug target receptors.

- The draft Guidance implies that safety assessment of all metabolites exceeding a certain threshold would be mandated. The guidance should clarify that only the primary or major metabolite representing a particular biotransformation pathway should be tested for toxicity. For example, if a unique human metabolite is determined to be safe and/or adequately investigated in additional nonclinical studies, then it can be assumed that downstream metabolites resulting from this same pathway are safe as well. Conversely, a primary metabolite that is tested and found to have clinically relevant toxicity would likely impugn its downstream metabolites via the same pathway without the need for actual safety testing.
- In the final guidance, a recommendation for a tiered evaluation of potential metabolite toxicity would be most useful. This assessment would consider whether the metabolite is stable or reactive and the potential site of action (i.e., on-target or off-target). For example, a pharmacology / safety pharmacology evaluation alone may be sufficient to evaluate a stable metabolite with on-target pharmacology viz. parent drug.
- The draft Guidance indicates that Phase II conjugates may retain pharmacological activity and may require toxicological evaluation. If pharmacological activity is at issue, this should be addressed through the dose escalation process in nonclinical and clinical studies (phase 1 and 2). Furthermore, there may be significant stability issues for synthetic standards of these Phase II conjugates, which may preclude availability of these metabolites for subsequent toxicity testing. Even if the conjugate was stable enough to dose, it may be impossible to get the exposure high enough to elicit toxicity, and the suggested parenteral administration of metabolites may result in a dramatically different distribution than after oral administration. The vast majority of Phase II conjugates generally pose no safety concern and the final guidance should enable the sponsor to evaluate these cases individually.
- With respect to genetic toxicity evaluation, we request clarification on the term "screen" from the text in lines 249-252. If the intent of the guidance is to conduct genotoxicity testing consistent with ICH guidelines and according to GLPs, the term "screen" could imply the use of abbreviated non-GLP versions of the standard tests. However, in certain cases based on feasibility (e.g., available quantity of synthesized or isolated metabolite, critical timing to progress of the clinical program), screening or non-GLP formats of the standard tests could be used to initially assess genotoxic potential of a selected metabolite of interest and be submitted for review. Also, if a suspect human metabolite can be generated from parent drug in the *in vitro* genotoxicity test systems through metabolic activation sources (e.g., induced rat S9), then qualification through this approach could be appropriate instead of testing the synthesized or purified metabolite directly.
- Also concerning genotoxicity testing, a positive response in one or both of the *in vitro* tests should be followed up according to ICH guidance, and should be generally consistent with approaches recommended previously by the agency in a draft

guidance (FDA CDER Draft Guidance for Industry: Recommended Approaches to Integration of Genetic Toxicology Study Results. Federal Register, Vol. 69, No. 231/70153. December 2, 2004. Docket No. 2004D-0493). We also believe that equivocal findings in an *in vitro* test may not be amenable to follow up assessment in cases where the *in vitro* results lack reproducibility, and therefore not require additional weight of evidence assessment.