



Global Research & Development

August 4, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Dockets Management:

Re: **Draft Guidance for Industry on Safety Testing of Drug Metabolites**
[Docket No. 2005D-0203, 70 *Federal Register*, 32839, June 6, 2005]

Pfizer submits these attached comments to the Draft Guidance for Industry on Safety Testing of Drug Metabolites, Docket No. 2005D-0203, 70 *Federal Register*, 32839, June 6, 2005.

We appreciate the opportunity to provide comments and commend the Pharmacology/Toxicology Committee for developing guidance on this topic. Additionally, we would invite direct dialog with the Agency if you would consider the opportunity valuable.

Sincerely,

A handwritten signature in cursive script that reads "Susan Mattano".

Susan S. Mattano, Ph.D., D.A.B.T.
Senior Director, Toxicology III
Pfizer Global Research and Development

General Comments:

We appreciate the Agency's expressed flexibility in considering relevant approaches to safety testing of metabolites on a case-by-case basis and willingness to engage in discussions early in drug development. There are four general topics on which we would like to comment, with additional specific comments on points in the guidance included below.

1. The starting point for evaluating and tracking of metabolites should be better defined. We suggest this to be the human radiolabel ADME study conducted to identify the metabolite profile.
2. We suggest that quantitation of a metabolite in circulation should be based on results for total drug related material obtained from the human metabolism study using radiolabeled drug.
3. Further clarification of what is considered sufficient to alleviate the need for additional toxicity testing (lines 24 and 184) is requested. We suggest that the demonstration of equal systemic exposure in humans and a single toxicology species would suffice.
4. We submit that the basis for the definition of a "major metabolite" warrants additional discussion. We feel the need to further refine the definition of a major metabolite is pivotal to the guidance, and therefore we encourage the Agency to delay issuing the guidance until additional opportunities are made available for open scientific discussions.

Specific Comments:

Introduction

Lines 24, 59: The second part of the definition of a "major metabolite" related to its presence at "much higher levels" in humans than in the nonclinical species is inconsistent with statements on Line 29, where a major metabolite is defined in terms of its presence at "sufficient levels to permit adequate evaluation," and Line 184 which obviates the need for further testing when systemic exposure to a metabolite is equivalent in humans and animals. We suggest that deleting the word "much" [line 24 and 59] would help to address the inconsistencies.

Line 28: The guidance focuses the designation of a "major" metabolite (i.e. one which requires closer examination for potential toxicity) on a percentage basis. The cutoff of 10% is derived from examples of drugs generating toxic metabolites that are 10% of dose or 10% of total circulating drug-related material (acetaminophen, felbamate).

We propose that, for some cases, particularly for compounds requiring relatively low doses, an alternate way of defining a major metabolite based on an absolute amount rather than a percentage might be more appropriate.

Further detail concerning application of an abundance-based approach to defining a major metabolite is included in a commentary recently accepted for publication in Drug Metabolism and Disposition and available electronically at <http://dmd.aspetjournals.org/papbyrecent.shtml>. We would welcome further dialog with the Agency on the approaches described in this publication as desired.

Lines 29 and 184: The definition of 'sufficient' in line 29 is later defined as 'equal' in line 184-5; we would suggest replacing 'sufficient' with 'equal' throughout the document for clarity.

We agree that this is the appropriate approach, as it is based on comparisons of mass rather than percentage. Thus, if a metabolite is observed in humans and satisfies the criteria for 'major' (described above), then the exposure to this metabolite in animals is assessed and if equal or greater, the animal toxicology studies have provided risk assessment for the metabolite. This will appropriately address those situations in which the percentage of a particular metabolite in animals is lower than in humans, but because animals are typically administered high doses in toxicology studies, greater exposure to the metabolite has been achieved in animals than in humans.

Background

Line 80: For clarity, delete "As a result,".

Line 83: While we agree that the halothane example cited is factually correct, we question its applicability. Halothane is administered by inhalation and ultimately large doses are administered. Further, in the clinic, the incidence of halothane-induced liver toxicity is low, and it appears to involve a reactive intermediate binding to a protein, which becomes an antigen. It is unlikely that standard nonclinical testing would have identified this risk.

Line 118: Some additional guidance on the "triggers" that point to a "reactive functional group" (i.e., selected alerting substructures, literature precedent, downstream metabolites such as a GSH conjugate, or the necessity to demonstrate reactivity experimentally) would be desirable.

Safety Testing and Nonclinical Design

Line 128: We suggest deletion of, or clarification of, the particular relevance of Bullets 1, 2, and 4 to the safety testing of drug metabolites. Further, Bullets 2 (significant toxicity) and 4 (irreversible toxicity...) seem redundant.

Line 134: We recommend changing the sentence to read: "The objectives of standard nonclinical safety studies are to evaluate the general toxicity profile of a drug and its metabolites in rodent and nonrodent animal species and to assess the potential for genotoxicity in support of studies in humans."

Line 149: While it is true that nonclinical studies will detect "potentially clinically relevant toxicity" that is related to the parent compound; in most of these cases it

would not be necessary to separately evaluate the safety of the metabolites. This investigation should only be necessary if the clinical toxicity is poorly monitorable and has serious implications to human safety.

Line 150: Testing of the metabolite in isolation from the parent may not represent the most relevant biological model. As an example, findings from such a study may not be relevant because the metabolite may not be able to penetrate target safety tissues from blood, but exhibits its effects when generated from the parent drug within the target tissue. Reactive metabolites (such as those arising from the cited examples (acetaminophen, felbamate, halothane, cyclophosphamide) will not be able to be directly administered to animals due to their chemical instability and administration of the adducted metabolite (e.g. mercapturic acid, etc) would not be adequate to address the direct toxicity of the metabolite. The situation in which it appears that a reactive metabolite is present in humans but not in the toxicology species poses a difficult challenge and a case-by-case approach may be needed, in consultation with the agency. The total mass of metabolite formed would be an essential part of this dialogue.

We therefore recommend that the sentence beginning on line 150 be stated more generally, for example: "In such cases, we recommend that the potential relationship between the toxicity and metabolites be evaluated."

Line 153: This statement is too general. Investigation using different routes of administration or alternative animal species is warranted only when significant differences in metabolite profiles are present, particularly given the statement in line 169.

Line 169: The connection between the first and second sentences in the paragraph is unclear and the sentiment is redundant with Lines 144-148. We therefore recommend deleting the two sentences beginning at Line 169.

Line 174: Consider substituting the word "considered" for "evaluated."

Line 184. We suggest that it is sufficient to demonstrate exposure equal to human in only one nonclinical species. All animal species will not provide a human metabolite profile, but it is likely that all human metabolites will be shown to occur in at least one animal species. This approach is similar to ICH Q3A recommendations for toxicological qualification of impurities in one species. Further, we submit that an *in vivo* assessment of clastogenic potential (through assessment of bone marrow micronucleus induction) in a metabolite-competent rodent species (such as rat or mouse) should also be considered as a genotoxicity qualification strategy if sufficient metabolite exposures are attainable. This may be conducted during routine general toxicity assessment of the parent drug. This approach also serves to assure that a suitable carcinogenicity test species exists that represents the selected metabolite of interest.

Line 194: We commend the agency's interest in encouraging submission of structure activity relationship analyses. We also submit that in certain cases a structure activity relationship analysis along with an expert- and/or literature-based risk

analysis could be sufficient to "qualify" a suspect metabolite without additional hazard testing.

Line 200: A brief statement in this section may be in order to describe the requirement for these studies to meet GLP requirements. One concern with the expectation for meeting GLP requirements is the potential for issues related to test article and/or formulations. With the concept that pivotal studies with metabolites should be run ASAP, depending on the chemistry involved, a balance between timing of study conduct and the capability of producing GLP quality test material in workable formulations with appropriate stability should be considered. Normally in compound development the time for bench chemistry to address these issues fits in the development program so that by the time GLP studies need to be run, appropriate processes for compound synthesis and analyses have been developed. With a metabolite program early in development, some of the GLP provisions may not be able to be met early on (e.g., full test article characterization, stability profiles in formulations). These of course can be addressed in the protocol and Compliance Statement, depending on how they may impact the study quality. If speed to study is the desire of the Guidance document, this too could be addressed so that sponsoring companies should know where to focus energy and resources. The risk of speed to study vs. quality of study needs to be considered and may vary depending on the metabolite and relative safety profiles of related structures.

Recommended Studies for Assessing the Safety of Metabolites

Line 236: The guidance to conduct studies using dose levels up to the elicitation of toxicity or to a maximum feasible dose seems to conflict with the statement in Line 184 that where systemic exposure to a metabolite is similar in humans and the animal toxicity models, additional testing may not be warranted. We suggest that metabolites should be tested to equivalency or an appropriate multiple (10X) of the human exposure. Exposure can be estimated by circulating concentrations of unbound drug or as total excreted metabolite or its subsequent metabolites.

Line 238: The recommendation to use an animal species most likely to maximize the potential to detect the toxicity of a metabolite is problematic. How would one know this? We recommend deleting this sentence.

Line 240: Direct administration of a metabolite in a toxicology study by the same route as the parent may not be appropriate for some orally administered drugs. Consideration of parenteral administration should be given in cases where exposure could be limited by poor absorption.

Line 249: In keeping with the overall spirit of this guidance document, we believe this section should be written to allow flexibility in genotoxicity testing. The use of the term "screen" in the first sentence implies the acceptance of abbreviated or modified versions of the standard tests, and some additional clarification would be welcomed. We feel that in certain cases based on feasibility (available quantity of synthesized or isolated metabolite, critical timing considerations in relation to progress of the clinical program) screening or non-GLP formats of the standard tests could be used to assess genotoxic potential of a selected metabolite of interest and submitted for

review. Also, we suggest that if a suspect human metabolite can be generated from parent drug in an *in vitro* genotoxicity test system using metabolic activation sources (induced rat liver S9 or related media from other species), this approach would be considered an acceptable method of directly testing the metabolite for genotoxicity. An 'exposure multiple' should not be required for *in vitro* genotoxicity tests since this test provides hazard identification but not risk assessment.

Lines 252-254: We submit that 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 suggest 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 do not require additional weight of evidence assessment.

Line 274: The use of alternative animal models such as transgenic models for carcinogenicity assessment should be included as acceptable alternatives to the 2-year bioassay.

Timing of Safety Assessments

Line 286. The sentences beginning "If toxicity studies..." and "In some cases..." appear to be redundant. We suggest deleting the first sentence.

Human ADME studies in which unique human metabolites are found and quantitated are usually conducted concurrent with Phase 2 programs. If a human metabolite were identified that required direct testing in safety studies, this could substantially delay Phase 3 testing. In keeping with the spirit of the Critical Path Initiative, we propose that in those instances where a human metabolite needs to be directly administered to animals for safety evaluation, or where long-term or carcinogenicity studies are warranted, these studies may be conducted concurrently with Phase 3 testing.

Appendix A:

The first level (left hand side) of the decision tree should be the following to be consistent with lines 184-186 of the guidance text: Animal \geq Human.