

Lilly Research Laboratories
A Division of Eli Lilly and Company
Greenfield Laboratories
P.O. Box 708
Greenfield, IN 46140
U.S.A.

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Phone 317 276 2000

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

Re: Docket No. 2005D-0203, Draft Guidance for Industry, Investigators, and reviewers: Safety Testing of Drug Metabolites; Federal Register Volume 70, Number 7, 70 FR 32839 (July 6, 2005)

Dear Sir/Madam:

The following comments on the above draft guidance are submitted on behalf of Eli Lilly and Company.

Sincerely,
Eli Lilly and Company



John L. Vahle, DVM, PhD, DACVP
Research Advisor, Toxicology
Eli Lilly and Company

2005D-0203

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General Comments

We support the overall intent of the Draft Guidance, especially as it relates to the Drug Metabolites in Safety Testing publication (Baillie *et al.* 2002). We recognize that a principal goal of the guidance is to focus on patient safety while minimizing unnecessary late-stage delays in drug development leading to product registration. However, we are very concerned that this guidance will ultimately delay drug approvals without ensuring additional safety by imposing rigid standards that do not account for the wide range of possible situations with unique and/or major metabolites.

Executive Summary

- We concur that further safety testing is not needed if a metabolite is present at sufficient levels in the standard nonclinical studies to provide an assessment of safety. The draft guidance needs greater clarity and consistency on this topic. The flow chart and certain sections of text suggests that further safety testing of all *major* human metabolites (however defined) would be required without considering relative exposure levels of these metabolites in the standard animal studies.
- The proposed >10% criterion for *major* metabolites is problematic from several standpoints (discussed later) and greater clarification is needed to define this threshold of concern.
- We do not find sufficient flexibility in the timing of submission of final metabolite toxicity study reports. It is our view that in many cases the benefit-to-risk profile for the molecule is sufficient to allow the conduct of metabolite safety studies in parallel with phase 3.
- Potentially clinically relevant toxicities are observed in the majority of standard nonclinical studies. The recommendation “to determine if metabolites contribute to that finding” (**lines 148-150**) implies that a direct correlation can be made between parent drug and/or its metabolite(s) and specific toxic endpoints. We request the removal of this recommendation from the final guidance.
- We believe that Phase II metabolites (conjugates) and potential reactive intermediates should be considered for metabolite testing on a case-by-case basis.

Assumptions

- We agree with the statement on **lines 169-170** that “it is uncommon for humans to form unique metabolites”, and we consider many of these recommendations reasonable if applied to those specific cases. Related to this, the proposed flow of the decision tree (**Appendix A**) indicates that even a unique human metabolite

must be >10% of the dose to be eligible for metabolite toxicity testing. This implies that unique human metabolites must *also* be major human metabolites, which should be explicitly stated in the text of the guidance.

- Similarly, we agree with the statement on **lines 184-186**: “If the systemic exposure in nonclinical species is equivalent to human exposure when measured in plasma and/or excreta, levels may be considered sufficient and alleviate the need for additional toxicity testing”. However, the decision tree in **Appendix A** incompletely captures this strategy by not clearly defining what “human > animal” means, and would require complete toxicity testing of metabolites >10% of the dose in humans regardless of any threshold of animal exposure. While the decision tree defines the extreme cases, we believe that it is inadequate to define actions pertaining to the intermediate cases where animal metabolite concentrations less than in human are acceptable from a safety perspective.
- **Lines 26-30** define major metabolites as those identified in human plasma accounting for >10% of drug-related material, based on administered dose or systemic exposure (whichever is less):
 - We request clarification on the qualifying statement: “whichever is less”. Assuming that the 10% trigger would be related to the most conservative estimate of human exposure, this should imply that a threshold *greater than 10%* would trigger additional testing.
 - The definition of *major* metabolite focuses on plasma; however, the statement on **lines 179-180** says that “excreted metabolite levels may be a more appropriate metric in many instances.” While the amount of excreted metabolite may be of value in characterizing the metabolism and disposition of the parent drug, we argue that circulating levels of metabolite(s) are most relevant in safety assessment and should form the basis for decisions to perform subsequent metabolite safety testing.
 - Since the recommendations in the Draft Guidance suggest identification of important plasma metabolites as early as possible, it is highly improbable that validated bioanalytical methods for all relevant metabolites will be available to support early (phase 1) clinical studies, nor would a human disposition study have been conducted. Thus, estimates of the metabolite concentrations are likely to be made based on LC/UV peak area or LC/MS ion abundance, which are *semi-quantitative*. We propose that a *relative ratio* of human vs. animal exposure to metabolites using a consistent analytical methodology should be used to provide a meaningful estimate of the relative abundance of any given metabolite without requiring validated bioanalytical methods or the conduct of a human disposition study before phase 2.
- In defining *major* metabolites, we propose that the systemic exposure method (based on metabolite-to-parent drug ratio across a defined time course) should be preferred over the % dose method because the circulating levels of a metabolite in plasma have a temporal component and the estimated % of dose may change as

a function of time. Overall, the guidance should be clear and specific regarding the method(s) proposed to calculate the appropriate threshold for drug-related material in plasma (**lines 26-30** and **lines 71-73**).

- **Lines 202-208** contain some excellent points to consider in the design of nonclinical studies to evaluate unique or major metabolites in humans, wherein it is acknowledged that the physicochemical characteristics, disposition, and biotransformation of a metabolite are likely to be different from the parent drug. Thus, it should be emphasized in the final guidance that the disposition of metabolites following direct administration may differ significantly from their disposition after parent drug administration and interpretation of the nonclinical and/or clinical relevance of any resultant metabolite toxicity may be confounded.
- We assume that the metabolism case studies (**pages 2-3**) have been highlighted to exemplify where metabolites present at <10% of the dose have been implicated in clinically relevant toxicity. We acknowledge that this situation occurs, but we do not think specific examples should be included in the final guidance.

Timing Considerations

- **Lines 286-288** recommend that final study reports on toxicity of a human metabolite be submitted to the Agency before beginning large-scale phase 3 trials. While there will be situations in which this precaution is warranted (*e.g.*, a reactive unique human metabolite with the potential for off-target toxicity), it is our view that this represents the rare exception rather than the rule, and it will often be acceptable from a benefit-to-risk perspective to complete the metabolite safety testing in parallel with phase 3. On-target toxicity will have been characterized in the animal models (even if the metabolite in question is not present) and on-target adverse events likely will be characterized through dose escalation in phases 1 and 2. A reasonable approach is to conduct the definitive [¹⁴C] human study at an appropriate time and then follow up with specialized metabolite testing once adequate test material is produced, characterized, formulated, and necessary bioanalytical methods have been validated. It would be common for these activities to extend beyond the initiation of phase 3; however, 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.
- **Lines 25-26, 68-69 & 166-167** suggest identification of unique or major metabolites in humans “as early as possible”. **Lines 284-285** similarly recommend that sponsors conduct in vitro studies to identify these metabolites. While it is indeed feasible for the sponsor to identify in vitro metabolites followed by an initial evaluation of the human in vivo metabolic profile in concert with the

single dose safety study, it is possible that both of these methods may overlook potential unique human metabolites (e.g., very polar Phase II conjugates) that are present at low levels in human plasma. We recognize that relying on the human [¹⁴C] ADME study data (presumably before phase 3) to establish the true nature and extent of potential metabolites for toxicity testing may pose downstream delays in drug approval; however, we are concerned that relying on data from very early studies has the potential to generate decisions in the selection of unique and/or major metabolites from an incomplete dataset and this situation might ultimately incur more delays in delivering medicines to the patient. While the final determination of which metabolites to test may rest on the results of a human metabolism study, the sponsors should be given flexibility in timing those studies.

Scope of Work

- In many cases, a biotransformation pathway may occur directly on parent drug (*i.e.*, primary metabolite), but this pathway may similarly occur on other primary metabolites leading to secondary metabolites, for example. This interdependent metabolic profile may produce *numerous* unique or major metabolites for potential toxicity testing. The final guidance should clarify that only the initial biotransformation product needs to be tested for toxicity, which should address the need for safety qualification of unique metabolic pathways resulting from direct metabolism of the parent drug.
- **Lines 112-116** indicate that some 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 parenteral administration of metabolites suggested on **lines 240-241** 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.
- The recommendation to test reactive metabolites is highly problematic. We cannot envision any criteria for defining exposure to these reactive metabolites, especially if they are unstable and difficult to trap. If the reactive metabolites stem from glutathione conjugation, it is impractical to test all the potential thiolated metabolites that may result. We request that these situations be handled on a case-by-case basis.
- **Lines 148-150** contains a statement that appears to be out of scope for the purpose of this Draft Guidance: "Additionally, when a potentially clinically relevant toxicity is observed during standard nonclinical studies, it is prudent to determine if

metabolites contribute to that finding.” The next statement on **lines 150-152** directs the sponsor to have the metabolites synthesized and directly administered for pharmacology/ toxicity testing. These recommendations imply insight or knowledge that the sponsor cannot possibly have regarding the relative contributions of parent drug and its various metabolites in eliciting clinically relevant toxicities at this stage of development. We suggest that these statements be removed from the final guidance.

- **Lines 196-198** suggest submission of structure activity relationship data relating to mutagenicity, carcinogenicity, and/or teratogenic potential of drugs and their metabolites, but indicate that these data are not a suitable substitute for actual testing. We request that the Agency clarify the reasons for requesting data that are not definitive.
- In general, the list of proposed nonclinical safety studies on important metabolites appears to be reasonable if a metabolite safety evaluation is warranted; however, we want to reemphasize that the design of the safety package for a given metabolite should be based on the relevant data. In addition, we suggest that genetic toxicity testing of metabolites (**lines 249-254**) with S9 activation in the standard battery is not warranted since this could convolute the genetic toxicity profile if irrelevant downstream metabolites were generated.