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

Re: **Docket Number [2005D-0203]**
Response to FDA Call for Comments
Safety Testing of Drug Metabolites

Dear Sir or Madam:

Reference is made to the June 6, 2005 Federal Register notice announcing the request for comments on Guidance for Industry – Safety Testing of Drug Metabolites

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Scott W. Grimm, Ph.D., Associate Director, DMPK, at 302-886-2271.

Sincerely,

Carol A. Stinson, Director Regulatory CMC
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CAS

Enclosure

2005D-0203

US Regulatory Affairs
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Cb

Draft Guidance
[Docket No. 2005D-0203] Safety Testing of Drug Metabolites

General Comments

- **Comment 1**

In today's climate of safety-related issues with drugs, it is easy to understand that the FDA would be concerned about drugs that have unique human metabolites or metabolites whose systemic exposure is significantly higher in humans than in non-clinical species used in safety testing. However, some of the recommendations in this draft Guidance (either explicit or implied) have raised concerns in AstraZeneca about their interpretation and usefulness. Moreover, because the recommendations described in this Guidance are somewhat vague and have the potential to increase significantly the overall drug development burden. In this sense, the recommendations seem to be inconsistent with the spirit of the FDA's Critical Path Initiative. The following comments outline a number of significant issues, which we hope the Agency will consider in developing the final guidance document on safety testing of drug metabolites. We also point out a number of inconsistencies or gaps in the document that need to be clarified to increase its usefulness. Finally, we include a number of conceptual ADME and other considerations that need to be accounted for in further developing the final guidance document. Some of these issues could, at times, make it impossible to adequately assess the safety of a metabolite that is generated following exposure to a parent drug.

- **Comment 2**

While the Guidance is described to be suggestive in nature, there is the implication that non-compliance with the recommendations could significantly delay a drug development program (e.g., see footnote #2 in the Guidance) or marketing approval and thus each case would require extensive discussion and negotiation on the testing decisions, strategy, and interpretation of metabolite investigations with the Agency. The final guidance should clearly state if these specific sponsor-agency dialogues are necessitated by this guidance to limit delays in drug development and approval.

- **Comment 3**

Many metabolites will prove to be extremely difficult to synthesize/manufacture in high yield, highly pure quantities (e.g. regiospecific ring-hydroxylated metabolites). Many metabolites, including by definition reactive metabolites, may also be unstable chemically thereby precluding toxicity testing of any duration. These synthetic issues may make it impossible to assess the safety of some metabolites.

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- **Comment 4**

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.

- **Comment 5**

The guidance should define the dosing strategy to be used – ie., to an MTD or to an adequate multiple of human exposure (“adequate” needs to be defined). This could have significant implications on compound requirements.

- **Comment 6**

Related to the comments on Section IV listed below, Safety Pharmacology other than ECG measurements was not specifically recommended in the Guidance. Section 2.F of Guidance for Industry: S7A Safety Pharmacology Studies for Human Pharmaceuticals (July 2001) suggests that major human metabolites not found or found in relatively low amounts in animals 'assessment of the effects of such metabolites on safety pharmacology endpoints should be considered'. Section VI of this guidance document should include safety pharmacology testing if that was the intent of these related guidances (referencing S7A). Otherwise, the omission should be explained to avoid confusion.

- **Comment 7**

Human ADME studies using radiolabeled compound to quantify metabolite exposures, are traditionally single dose studies. Metabolite:parent exposure ratios may be different after chronic dosing than after a single dose due to the kinetics of their elimination. These study conditions used for metabolite exposure analysis should be considered in the decision to evaluate the toxicity of a “major” human metabolite, the final Guidance should consider.

- **Comment 8**

The Guidance should include the evaluation of secondary metabolites observed in metabolite profiles in the nonclinical safety species to indicate that a particular primary metabolic reaction occurred and therefore at least the liver was exposed.

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- **Comment 9**

In making a decision to evaluate a “major” metabolite, the final Guidance might also consider the potential differences in unbound concentrations of metabolite across species due to variation in plasma protein binding.

- **Comment 10**

The Guidance does not distinguish between oxidative and conjugated metabolites. In general, conjugated metabolites are more polar and should be less of a toxicology concern than parent or oxidative metabolites, and many would not be stable under conditions of oral administration. Because it is recognized that there are exceptions to this generalization, the situation should be evaluated on a case-by-case basis.

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Section	Page or Line Number	Comment or proposed replacement text
II	2, Line 71-81	Major metabolites worthy of consideration for safety assessment are defined in the Guidance as those “constituting >10% of drug related material in human plasma (by systemic exposure (AUC) or administered dose)”. As currently written, this criteria is confusing as fraction metabolized or percent of dose is typically determined for excreted metabolites, not circulating metabolites. The final Guidance should clarify the recommendations and preferably focus on concentrations of metabolite present in blood or plasma. If this is not possible and the Guidance proposes quantitative analysis of excreted metabolites as an alternate, then it should be recognized the excreted metabolites may be more indicative of a pathway, than an individual circulating (and therefore potentially toxic) metabolite. Pharma sponsors and the agency should alternatively consider developing a threshold criteria based on the mass of the dose of parent drug, since the absolute exposure (metabolite abundance) achieved using the 10% criteria will vary significantly depending on the size of the administered dose.
II	2, Line 80-81	The Guidance states “some metabolites at less than 10 percent should also be tested”. This statement leaves it unclear under what circumstances a sponsor should test a minor metabolite and should preferably be removed from the guidance.
II	Page 2 , Line 83-103	On pages 2 and 3, four examples are given to support the choice of the 10% cut-off. However, the toxicity of the exemplified drugs is believed to be due to reactive metabolites, which typically cannot be measured in plasma. Two of the examples were of metabolites found in urine and therefore do not support the notion that plasma exposure is the important measurement of systemic exposure. The final guidance should clarify why the chosen examples were used and

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		how sponsors should interpret this. Otherwise, the examples do not help clarify the recommendations or thresholds.
III	Line 148-153	The Guidance states, " when a potentially clinically relevant toxicity is observed during standard nonclinical studies, it is prudent to determine if metabolites contribute to that finding." This statement appears to suggest that sponsors should determine the mechanism of any toxicity seen in the preclinical studies, ie whether it is due to any of the metabolites.
III	Page 4, Lines 170-172, 184-186	The Guidance should be clear when safety testing should occur for a "major" or >10% metabolite, i.e., what ratio of exposure in human vs. safety species would signal the need to consider safety testing.
III	Page 4, Line 175-180	The Guidance should further specify the reasons for measuring metabolites in excreta as a criteria for deciding to conduct safety assessment studies since we do not agree that excreted metabolites are quantitative indicators of systemic exposure. The draft guidance states that it can be assumed that a metabolite present in excreta has been exposed systemically. However, metabolites with high concentrations in urine but very low in plasma are not uncommon. This may occur for polar, soluble metabolites that are excreted rapidly so that concentrations in plasma do not accumulate. Another example is when a metabolite is formed in liver and excreted via bile – liver and intestine will be exposed to the metabolite but not other tissues. We believe the Guidance should focus on metabolites found in the human systemic exposure that are believed to be inadequately characterized with regard to their safety in a preclinical species.
IV	6	<p>Section IV of the draft Guidance recommends 4 kinds of safety studies to assess the safety of a unique or major metabolite. Some minimum study duration recommendations are outlined but then vague, case-by-case, possibilities for conducting investigations of much greater duration are included. The circumstances under which the more extensive work would be done are not clear. In fact, the factors outlined in the Guidance that would lead to a requirement to do these studies will be met in the majority of drug development programs (e.g., reproductive toxicology studies when a drug will be used in women of child-bearing potential, or long-term carcinogenicity studies when in silico predictive tools give a structural alert).</p> <p>AstraZeneca believes it should be possible to assess toxicity of the metabolite, particularly "major" metabolites on a more limited basis with an abbreviated test battery. Metabolites may be stable or be chemically reactive/unstable. Furthermore, metabolites may exert biological effects through target-related (suprapharmacology at the intended target in a tissue of interest or act at the target receptor in a</p>

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		<p>non-therapeutic tissue), non-target related (similar receptor/target family or totally different receptor/target), or through chemically mediated (covalent binding, reactive oxygen, etc) effects. Consideration should be given to develop a tiered evaluation of the potential toxicity of a metabolite, taking into account whether it is a stable or reactive metabolite, and the potential site of action. For example, a pharmacology / safety pharmacology evaluation alone could be sufficient for a stable metabolite which interacts with the same target as parent drug.</p>
IV	Lines 202-204	<p>The disposition (tissue distribution and exposure profile) of a metabolite dosed orally or parenterally will be inherently different from a metabolite generated in the liver or other metabolically competent tissue. This fact makes the interpretation of metabolite toxicology data very difficult and possibly irrelevant to assessing human safety of a drug candidate. As a simple hypothetical example, a synthesized metabolite dosed orally might cause GI toxicity due to the high luminal concentrations of the molecule. Conversely, an orally administered synthetic metabolite may be rapidly metabolized (or not absorbed) such that relevant exposure margins cannot be achieved. Therefore, assumptions about the disposition of an administered versus biologically generated metabolite need to be clearly understood and accounted for in the interpretation of study results and the assessment of risk to humans. The guidance should adopt a “best diligence” approach where the safety testing of metabolites proves very difficult due to the characteristics of the synthetic metabolite and its dispositional characteristics upon oral or parenteral administration. The Agency should also be flexible enough to discount toxicological effects that may be related to the route of administration.</p>
IV	7, Line 267-77	<p>Carcinogenicity Studies - Experience leads industry to believe that in silico predictors have utility as ‘eye-openers’, highlighting areas for increased vigilance. However, using QSAR structural alerts as one of the primary reasons for having to conduct carcinogenicity studies is not reasonable, since the in silico tools in common use in industry produce a significant number of false positives.</p>
Glossary	Line 301	<p>The second half of this definition is missing: “... and present at low levels in animals” should be added.</p>

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Decision Tree	Line 352-356	The path "Identify metabolites" -> "Human only" -> "H>10%" -> "Metabolite Characterization" is not stated in the Guidance text. This is the only statement in the Guidance that a human unique metabolite should only be characterized if it is >10% of the dose. This should be clarified in the final guidance since the impression from the text is that human unique metabolites always need to be characterized no matter at what level it is formed.