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Boehringer Ingelheim
Pharmaceuticals, Inc. □

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

July 29, 2005

**Docket No. 2005D-0203, Draft Guidance for Industry on Safety
Testing of Drug Metabolites**

Brian Walter, Ph.D.
Telephone (203) 798-4871
Telefax (203) 778-7880
E-Mail [bwalter@rdg.boehringer-
ingelheim.com](mailto:bwalter@rdg.boehringer-
ingelheim.com)

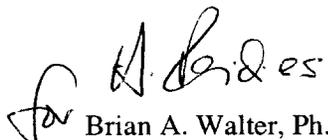
900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Sir or Madam:

Boehringer Ingelheim appreciates the opportunity to give comments on the above-referenced draft guidance. Our comments are provided on the following pages.

Please contact me with any questions or comments on this correspondence.

Sincerely,


for Brian A. Walter, Ph.D.
Senior Associate Director
Drug Regulatory Affairs

2005D-0203

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Boehringer Ingelheim comments on:

FDA Draft Guidance for Industry on Safety Testing of Drug Metabolites

Consideration should be given to the following:

- With increasingly potent compounds, e.g. CNS therapeutic area, a level of 10% of active metabolite would have to be extremely potent to be toxic. If this increased potency lacks specificity, some indication of toxicity related to Pharmacological potency will be generated through receptor/channel screening.
- With increasingly potent compounds there will be significant challenges in determining 10% levels of metabolites.
- Should these criteria apply to all modes of administration? For example, pulmonary drugs are administered to the site of action and while a percentage of the administered dose is orally ingested, the overall result can be a low exposure. Using these same criteria adds an unnecessary level of complication.
- Most of the examples provided in this document as being active at less than 10% are compounds that generate reactive intermediates. Since there is not a 'linear' relationship between reactivity and the toxic effect, we should not be establishing criteria based on this subclass of metabolites. The industry in general is screening for reactive intermediates as a separate endpoint and in many cases is already 'identifying' the reactive species. Additionally, quantitation of these reactive species is not a good indicator of the amount that was generated.
- The guidance lacks clarity around the use of structural alerts as a trigger for safety testing. For complex endpoints such as cancer and reproductive toxicity, the validity of many structural alerts is questionable and substantial reliance on these alerts as a trigger may not be warranted.
- The difficulties of chemically synthesizing metabolites should not be ignored. If the industry is required to generate metabolites at less than 10%, this will increase the need to synthesize metabolites such as glucuronides that can be very challenging. This could be considered as a significant waste of resources.
- Additionally, if the metabolite is a conjugate such as a glucuronide, is testing recommended for the unconjugated product, the conjugate or both?
- Administering certain metabolites by the 'preferred' route of administration will provide significant difficulties for oral dosing, e.g. conjugates (absorption, cleavage by gut flora).
- The PK of metabolites can be significantly different when administered directly. Attaining required AUC levels could provide significant challenges.

Boehringer Ingelheim comments on:
FDA Draft Guidance for Industry on Safety Testing of Drug Metabolites

Some more specific comments:

- Line 118-120 This statement on reactive metabolites is vague and should not be included in this guideline as the agency cannot use this information to determine the potential outcome of having a reactive metabolite.
- Line 144 Clarify that this refers to in vivo metabolite id.
- Line 147 'appreciable levels' is vague. Appreciating the difficulties in stating levels of significance, can the agency suggest some clearer guidelines?
- Line 148-152 If the metabolites are present in studies evaluating toxicity of administered parent compound, is the agency requesting that these studies be repeated with metabolite alone? If there is adequate exposure in the original study with dosing of parent, then metabolite related toxicities should be observed.
- Line 167 Would the agency comment on their reliance on metabolite id in humans with non-radiolabeled compounds vs more definitive human ADME studies?
- Line 177 Consider addressing the issue of metabolites found only in feces but not circulating. Would the 10% value still apply since there would be limited exposure. Is there a need to qualify this statement?
- Line 301 Does the 10% value relate to C_{max} or AUC? The latter provides a more complete assessment. Should this criterion be restricted to plasma or include excreta which would give a time-averaged level of metabolites.