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

Re: Docket No. 2005D-0203; Draft Guidance, *Guidance for Industry, Safety Testing of Drug Metabolites* [70 Federal Register 32839 (June 6, 2005)]

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the **Draft Guidance, *Guidance for Industry, Safety Testing of Drug Metabolites*** (June 2005). Our company's mission is to extend and enhance human life by providing the highest quality pharmaceutical and related health care products. We have a deep commitment to the appropriate safety evaluation of our drugs. For these reasons, we are interested in commenting on the Draft Guidance. Our comments are set forth below.

General Comments on Proposal

We commend the FDA for the efforts it is making toward providing guidance to industry on the issue of safety testing of metabolites of new chemical entities. There are, however, several aspects of the proposed guidance that are unclear in the current draft, and other aspects that risk prescribing excessive testing and other actions that could impede new drug development and are contrary to the FDA's critical path initiative.

The major concern we have with the document is that it appears to treat all metabolites in a generic fashion, regardless of their chemical nature. As metabolism of certain compounds to produce reactive metabolites is thought to play a role in the toxicity profile of those compounds, we share the concern over this type of behavior in our new drugs. Indeed, the draft guidance uses several examples of drugs where a reactive metabolite is thought to be formed and produce toxicity, and we agree that careful characterization of the metabolite pathways in these cases would be warranted. However, the vast majority of metabolites encountered during drug development are not reactive in nature and often have little or no pharmacological activity. As written, the Draft Guidance appears to make *no distinction* in how a sponsor would characterize these two very different classes of metabolites. If sponsors are required to apply the strict standards for metabolite characterization laid out in the Draft Guidance in all cases, then there

will be a significant impact on the drug development process. Based on the limited benefit of this information (especially for metabolite molecules with low potential for pharmacologic or toxicologic interactions), these considerations seem to be at odds with the FDA's critical path initiative as well as efforts to limit use of animals. There are also a number of specific places in the document where there are significant concerns that we feel need to be addressed. These concerns are outlined below.

Specific Comments (Items that Need Clarification & Recommended Actions)

A) Introduction

- 1) It should be stated clearly that the importance of the specific properties of a metabolite must be considered during the evaluation phase. If there is little chance for the metabolite to contribute to the overall toxicology/pharmacology of the parent (e.g. stable, non-pharmacologically active metabolites), then there should be a statement that the recommended path for further actions is distinct from metabolites that are of legitimate concern, as long as the metabolite is present at some level in the toxicological species.
Recommendation: A statement that clarifies the distinction between different classes of metabolites should be added.
- 2) The draft guidance includes a justification of a "10% of drug related material" threshold level for safety assessment consideration. This level of characterization is based on comparisons to several reference compounds that form high levels of reactive species. Although the flux of parent compound through a pathway that yields a reactive species is approximately 10% for all the compounds cited, the amount of reactive species or product of a reactive species that could be detected in plasma, urine or feces is far different. As this guidance is aimed at detection of metabolites in these matrices, it is hard to justify the selection of these examples as the basis for setting a threshold level.
Recommendation: Additional rationale for the selection of 10% as the threshold level should be provided.
- 3) The two concepts of "percent dose" and "systemic exposure" should not be interchanged as methods to characterize a metabolite, especially not in the same sentence. The attempt to incorporate both "systemic exposure" and "percent dose" as parameters in assessment of exposure to metabolites is an important consideration; however, as the guidance is presently written, it is unclear exactly how these parameters are to be used. As currently phrased "administered dose or systemic exposure *whichever is less*" (Lines 28-29), the draft seems to imply that, for example, metabolites circulating at very high concentrations, but constituting very small fractions of the total dose based on recovery in excreta would not be of concern.
Recommendation: Additional clarification on the use of "percent dose" and "systemic exposure" to characterize metabolites should be provided.
- 4) The statement "major metabolites...and were not present at sufficient levels to permit adequate evaluation" (Lines 27-30) needs further characterization. As stated in the flowchart later in the document, all metabolites that are deemed major in humans must be represented in the toxicology species at concentrations greater than those in humans. This

is an extremely difficult hurdle to meet for every metabolite, especially for highly metabolized compounds. Are exposures in animals to stable, non-pharmacologically active metabolites sufficient where the exposure ratio relative to humans is <1 but where the metabolite is clearly present in animals? Is there a more reasonable measure of relative exposure that defines the metabolites as non-unique but does not require a multiple of >1 ? How can exposure in animals as based on presence in bile or urine be used as a comparator to human plasma exposure?

- B) Line 71. The argument for study of metabolites that constitute 10% or greater of the administered dose is made without consideration of dose. The examples cited are all relatively high dose compounds (>100 mg), and this produces a substantial body burden of these reactive metabolites. The situation for drugs administered at relatively low doses will be significantly different.

Recommendation: Language that describes a reasonable course of action for compounds based on the daily dose of parent compound should be included.

- C) Line 114: should read ‘ *Some* sulfate and glucuronide metabolites....’

- D) Line 118 should read “...metabolites are suspected to contain a reactive functional group *unique to the metabolite, ...*”

- E) Line 183. Development of analytical methods. Although there have been significant advances in methods of detection, the development and deployment of validated GLP methods for analysis is still a resource intensive practice.

Recommendation: There should be additional guidance as to whether non-GLP analyses could be employed as methods to allow decision making on the importance of metabolites. Also, suggested practice on the number of studies in which metabolite exposure should be monitored would be helpful; e.g. it seems reasonable to measure the exposure of key metabolites in select human and animals studies rather than monitoring throughout the entire development program.

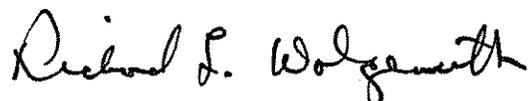
- F) Lines 196-198. “Although structure activity relationship analyses are not considered a substitute for actual testing, we encourage submission of the results from these analyses.” In addition to structure-based analysis, guidance on the acceptability of other forms of information such as a review of scientific literature or consultation with recognized expert should be provided.

- G) Line 202. “it is important to consider the physicochemical characteristics of the metabolite...” It is exactly these considerations that make it difficult/impossible to administer many metabolites of concern directly to animals. In none of the examples given to justify the direct study of metabolite would it be possible to directly study the toxicity of the metabolite in question. By nature the metabolites we are most interested in characterizing do not lend themselves to study in the fashion described. The metabolites that are amenable to this type of study are of much less overall concern.

- H) Line 211. " A pharmacologically active metabolite can be more, equal or less active than the parent drug....." This statement should be clarified as it could apply to all metabolites.
Recommendation: BMS suggests that when a metabolite reaches some reasonable level of activity relative to parent (e.g. 10-fold less active), it should *not* be considered as an active metabolite.
- I) Lines 249-252. Please clarify the use of the term "screen."
- J) With regard to follow up on equivocal and positive in vitro genotoxicity findings, BMS suggests that a positive response should be followed up in accordance with ICH guidelines and consistent with recently issued draft guidance on the integration of genetic toxicology results (12/2/2004). We also suggest that no additional tests may be required for equivocal in vitro findings if they are not reproducible.
- K) Timing of Safety Assessments. The draft guidance urges sponsors to identify unique and major human metabolites as early as possible in drug development and requires that preclinical reports be submitted prior to phase 3 trials. This may not always be achievable without a significant delay to the development timelines. Once a unique/major metabolite is identified, considerable effort and time may be required to synthesize/stabilize metabolite; develop GLP-compliant analytical methods (for bulk metabolite quantitation and plasma analysis); and conduct and report studies.
Recommendation: The Agency should consider linking the timing of safety assessments with the degree of toxicologic concern for the metabolite.

BMS appreciates the opportunity to provide comment and respectfully requests that the FDA give consideration to our recommendations. In light of the potential profound effect of the recommendations contained in the draft guidance on the speed and cost of effective drug development, we suggest that further dialog take place among experts and the Agency, and that a second draft be prepared based on comments received prior to finalization of a guidance. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



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