

August 4, 2005

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

Re: Comments on draft Guidance for Industry on Safety Testing of Drug
Metabolites. Docket No. 2005D-0203

Dear Sir/Madam:

The following comments on the draft guidance are submitted on behalf of Novartis pharmaceuticals. Novartis Pharmaceuticals corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ more than 78,000 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

The publication "Guidance for Industry: Safety Testing of Drug Metabolites" addresses the need to identify, characterize and evaluate the safety of unique major human metabolites, which may not be adequately assessed during standard nonclinical studies. The guidance further recommends specific studies for assessing the safety of metabolites and their timing in the drug development process. The document emphasizes that the identification and understanding of human metabolism early during drug development is important for the overall safety assessment. We are in agreement with many of these points although some may require further clarification or deserve additional discussion. Please see below our comments for your consideration.

1. Clear definitions of 'unique' , 'sufficient level' and 'higher level' of a human metabolite

In the introduction it is stated that the guidance deals with 'unique' and 'major' human metabolites not present at sufficient levels in animals. Nevertheless the document also suggests that contributions of metabolites to toxicity should be

assessed regardless of the metabolite being unique (lines 148-155). It is not clear what are sufficient levels of metabolite exposure in animals compared to humans which would preclude further testing in animals. In addition, a better definition on 'much higher level' (line 24) and 'present at sufficient levels' (line 29) would provide more clarity. Similarly, clarification is also needed whether a major metabolite is determined from the exposure or from percent dose as measured from the excreta.

2. Reactive metabolites versus major metabolite and 10% (of dose or systemic exposure) threshold

Using four examples, the guidance points out that metabolites even with low exposures (<10%) can be responsible for significant toxicities. In all these examples toxicity is due to a reactive metabolite, which are often short lived and not directly detectable. In addition, in the examples chosen, the metabolites are not species specific and their toxicity would have been assessed in animal studies.

Formation of reactive metabolites can be inferred from trapped products, however the reactive intermediate cannot be readily synthesized for testing. In addition quantitation of exposure to reactive chemical species is difficult and may under-represent the actual value. Thus a threshold of 10% (of the dose or systemic exposure) for additional toxicological testing should only be applied for those metabolites which are at significantly lower levels (to be defined) in the toxicological species and where the metabolite has a structural alert or exhibits pharmacological activity. Testing of the stable end product of a metabolic pathway involving reactive metabolites is meaningless as it does not test for the reactive intermediate. Therefore, we suggest that a case by case assessment should be made considering multiple factors versus a defined threshold.

It is important to note that metabolism is generally a detoxification process leading to more polar structures which are less likely than the parent compound to bind to e.g. receptors, and/or be toxic and generally have a lower volume of distribution. It is more the exception, rather than the rule, that metabolites are more toxic. In most of these cases, toxicity results from reactive metabolites which can be deduced from in silico investigations (structural alerts) or inferred from the overall metabolite pathway. In the case of pharmacologically mediated effects the pharmacological activity of the metabolite could readily be assessed in vitro. Testing of 'benign' metabolites does not improve to the overall safety, while it uses resources which could alternatively be used to advance the development of other important therapies. Furthermore, it would delay initiation of pivotal trials, increasing development time. As such it is contrary to the spirit of the Critical Path Initiative.

In summary, the guidance needs more clarification in some essential points and is not balanced in its presentation. It focuses on the testing without a clear recognition that if the metabolite in humans is present in similar or greater concentrations in animals then safety has been appropriately addressed. Also, a 10% value is arbitrary and metabolite testing makes only sense when huge differences in exposure exist

between animals and man and in addition if there are compounding issues such as pharmacological activity or structural alerts. A consensus on an appropriate safety margin for a potentially toxic metabolite remains to be established and could be the topic for a science based workshop.

Novartis Pharmaceuticals is grateful for the opportunity to provide comments and offer suggestions and hope that the FDA will consider our response when publishing the final guidance for the use of public in the near future.

On behalf of Exploratory Development at Novartis

Sincerely,
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