



Schering-Plough

3032 5 AUG 10 A9:46

Integrated Therapeutics Group, Inc
700 Rockville Pike Suite 525
Rockville, Maryland 20852
Telephone (301) 770-9524

August 9, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20857

Re: Docket No. 2005D-0203 Draft Guidance for Industry: Safety Testing of Drug Metabolites

Dear Sir/Madam

Schering-Plough has reviewed the above referenced Draft Guidance, and we offer the following comments for your consideration.

I. INTRODUCTION

Lines 26-30:

“This guidance defines *major metabolites* primarily as those identified in human plasma that account for greater than 10 percent of drug related material (administered dose or systemic exposure whichever is less) and that were not present at sufficient levels to permit adequate evaluation during standard nonclinical animal studies.”

Please clarify whether this means that metabolites are only considered to be major if they are greater than 10 percent and not present at sufficient levels in animals?

II. BACKGROUND

Lines 71-73:

“Generally, we recommend that metabolites identified in human plasma that account for greater than 10 percent of drug related material (administered dose or systemic exposure whichever is less) be considered for safety assessment.”

The meaning of this sentence is unclear. We understand that a metabolite representing more than 10% of the circulating drug-related material should be considered for safety assessment. But should a metabolite be considered for

2005D-0203

C11

safety assessment when present in human plasma at less than 10% of circulating drug-related material but more than 10% of the administered dose as measured in the excreta? Does the criterion of >10% apply to a single dose or to multiple dosing at steady state? What does the phrase “whichever is less” mean? One of the percentages is based on dose and the other on plasma AUC, so there is no obvious way to compare the different measurements. A working example would be helpful to allow Sponsors to apply this point of the guidance.

III. SAFETY TESTING AND NONCLINICAL STUDY DESIGN

A. Goals of Safety Testing

Lines 148-152:

“Additionally, when a potentially clinically relevant toxicity is observed during standard nonclinical studies, it is prudent to determine if metabolites contribute to that finding. In such cases, we recommend that the metabolites be synthesized and directly administered to the appropriate animal species for further pharmacological/toxicological evaluation.”

The objective of standard general toxicity testing is to define the toxicity by escalation of doses until toxicity is observed. Furthermore, every preclinical toxicity is potentially clinically relevant. Thus, as written, the Guidance indicates that in essentially all cases, it will be necessary to synthesize and directly administer the metabolite for pharmacological/toxicological evaluation. However, we believe that the Guidance actually intends that direct administration would only be recommended in cases in which animals were underexposed to the metabolite during dosing of the parent only. Is this interpretation correct?

B. Identification of Metabolites

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.”

This sentence is unclear, because most scientists interpret the term “systemic exposure” to refer to metabolites circulating in the plasma, not to metabolites only observed in the excreta. Does this sentence mean that metabolites not circulating in animal plasma but excreted in substantial amounts in bile or urine could be considered equivalent in exposure to circulating human plasma metabolite levels?

IV. RECOMMENDED STUDIES FOR ASSESSING THE SAFETY OF METABOLITES

A. General Toxicity Studies

Lines 237-239:

“We recommend performing the study in the appropriate animal species most likely to maximize the potential to detect the toxicity of a metabolite”.

Since it is not possible to know *a priori* which animal species is likely to be most sensitive, is it necessary to conduct exploratory toxicity studies with two species in order to determine their relative sensitivities before beginning full assessment in the most sensitive species?

V. TIMING OF SAFETY ASSESSMENTS

Lines 284-288:

“Sponsors are encouraged to conduct in vitro studies to identify and characterize unique human or major metabolites early in drug development.”

In vitro studies do not reliably predict major human metabolic pathways. Therefore, how should the sponsor interpret and act on the results of a prospective in vitro metabolic profile before the results have been confirmed in vivo?

Lines 286-293:

“If toxicity studies of a human metabolite are warranted, we recommend studies be completed and the study reports be submitted to the Agency before beginning large-scale phase 3 trials. In some cases, it may be appropriate for these nonclinical safety studies with unique human metabolites to be conducted before phase 3 studies; for example, (1) if the metabolite belongs to a chemical class with known toxicity; (2) if the metabolite has positive structural alerts for genotoxicity, carcinogenicity, or reproductive toxicity; or (3) if clinical findings suggest the metabolite or related compounds have indicated special clinical safety concerns, such as QT prolongation.”

The first and second sentence in this passage are somewhat redundant in that both suggest that safety evaluation of metabolites should occur and be submitted prior to the initiation of Phase 3. What is the distinction between the two sentences?

GLOSSARY

Lines 307-308:

“Pharmacologically active metabolite — A metabolite that has pharmacological activity at the target receptor that is greater than, equal to, or less than the parent compound.”

According to this definition, every metabolite is pharmacologically active, since every metabolite has greater, equal or less activity than the parent.

APPENDIX A: DECISION TREE FLOW DIAGRAM

Presuming that a unique metabolite present at less than 10% does not require safety testing (barring special situations such as a strong structure alert), the flow diagram should show an arrow going from the box labeled “Human Only” to the box labeled “H< 10% Dose”.

In addition to these comments that we have provided, we fully support the comments provided on this draft guidance by PhRMA on behalf of its member companies. Schering-Plough thanks you for the opportunity to present our comments.

Sincerely,



Gretchen Trout
Director, US Regulatory Liaison & Policy