



Pharmacia & Upjohn

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

18 February 2000

RE: Docket No. 99D-5047
Draft Guidance for Industry: *Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*

Dear Sir/ Madam,

Pharmacia and Upjohn has reviewed the draft guidance entitled, "*Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.*" Our comments are attached.

Should any clarification of our input be required, please don't hesitate to contact Jenny Peters at (616)-833-8141.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Jenny L. Peters
Director Global Regulatory Intelligence

99D-5047

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Comments about the Draft Guidance for Pharmacokinetic Studies in Patients with Impaired Hepatic Function

We found this draft guidance to be well written, providing generally rational recommendations on study design, interpretation, and subsequent product labeling for PK studies in hepatic impairment. We are concerned, however, about the fourth paragraph on page 4, Section A, Reduced Study Design, *I. Study Participants*:

A primary goal of this guidance is to provide recommendations on determining whether the PK and/or PD of a drug and its active metabolites are altered to such an extent that the dosage should be adjusted for patients with impaired hepatic function compared to the population for which the drug is intended. For this reason, the control group should represent the patient population with normal hepatic function, not necessarily young healthy volunteers. To the extent possible, the control group should be similar in age, weight, and gender to the hepatically impaired group. Other factors with significant potential to affect the PK of a drug (e.g., diet, smoking, alcohol intake, concomitant medications, ethnicity) should be considered, depending on the drug. For drugs known to exhibit genetic polymorphism (e.g., CYP2D6 or CYP2C19), the sponsor should consider the metabolic status of the enrolled subjects when analyzing the results of the study. ...

We consider these to be potentially conflicting goals unless certain demographic features of the hepatically impaired group (e.g., age, weight, gender, ethnicity, etc.) also represent the demographics of the intended patient population. Perhaps the intent is to assure heterogeneity encompassing the patient population, especially in the control group. However, with such small numbers (ca. 8 per group), this may be difficult to accomplish. It is also stated that factors with potential to affect PK should be considered. By considered, is it meant that they should be eliminated or that there should be a subgroup analysis of such factors? Again, it would be difficult to do the latter with the typically small numbers of subjects in these studies. Clarification of these issues is recommended.

A minor comment:

Page 10, Section A, Clinical Pharmacology Section, 1. Pharmacokinetics: Recommend wording for the third bullet point to reflect disposition of active metabolites, not all metabolites.

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