

# Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000 609 252 4000

January 31, 2000

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

**Re: Docket No. 99D-5047; Draft Guidance, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, 64 Federal Register 68357(December 7, 1999)**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1999, pharmaceutical research and development spending totaled \$1.8 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal which outlines when studies are recommended to assess the impact of hepatic impairment on the pharmacokinetics (PK) and, where appropriate, the pharmacodynamics (PD) of drugs or therapeutic biologics.

We commend the U.S. FDA for their discussion of this complex field and in particular its review of continuous variables, categorical variables, and marker substrates in the assessment of liver function. We agree that the Child-Pugh classification is the most appropriate choice in assessing liver function and appreciate the flexibility to use other additional surrogate markers when appropriate. Also, we commend the FDA for its general guidance about when studies are and are not necessary as well as for its clarification of the three study approaches (reduced study design, full study design, and population PK approach). However, there are several aspects of the proposed guidance that either appear contrary to the FDA's stated objectives or would benefit from clarification, which we have cited below:

99D-5047



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## **I. Elements Which Need Clarification or Modification**

### **(A) Significant Hepatic Drug Metabolism**

The draft guidance recommends that a hepatic impairment study be conducted if hepatic metabolism and/or excretion are greater than 20%. This cutoff seems conservative particularly for drugs with high intersubject variability.

“This guidance recommends a PK study in patients with impaired hepatic function if hepatic metabolism and or excretion account for *a substantial portion...*”(page 3, 2<sup>nd</sup> line)

**Recommendation:** We would suggest FDA elaborate on how this cutoff was developed and replace “a substantial portion” with an actual figure.

### **(B) Control Subjects**

Our impression from the draft guidance is that healthy subjects should not serve as control subjects. Rather, the control population should be the patient population for which the drug is intended (who also do not have liver disease). We are, however, unaware of evidence suggesting that hepatic metabolism and or excretion differ between healthy volunteers and patients without hepatic impairment. Further, it may be very difficult to recruit a group of control patients where other confounding factors, particularly concomitant treatment regimens, are not present. In our opinion, matching for age, gender, and weight in volunteers or patients should be sufficient.

**Recommendations:** FDA should consider making recruitment of patients an option but not a mandate for the control group and clarify the criteria for when use of patients is preferred.

### **(C) Drug Administration Section**

This section does not discuss route of administration. If two routes are proposed, the primary route intended for the bulk of the commercial use should be the one used for study.

**Recommendations:** We suggest FDA comment on route of administration and provide guidance regarding its preference regarding testing when both an oral and intravenous preparation will be commercially available.

### **(D) Sample Collection and Analysis Section**

#### **Sample Times**

The recommended sample collection times to determine the elimination half-life should be adequate to calculate the elimination half life whenever possible. There will be cases, however, where a prolonged terminal phase will occur.

**Recommendation:** In the instance when a prolonged terminal phase occurs, it would be advisable to have the flexibility to collect samples over a shorter interval that still adequately represents the profile (i.e. 80% of the AUC at infinity) and allows assessment of the impact of impaired hepatic function on the elimination phase.

### **Measurement of Free Fraction**

The guidance implies that drugs with protein binding of 80% or greater are considered extensively bound. It recommends determination of the unbound fraction at peak and at trough times.

**Recommendation:** We would like justification for the selection of 80% protein binding as a criterion for an extensively bound drug. Clarification is also sought regarding how the fraction unbound is to be determined. For example, should this be measured in subject samples following drug administration (which may be altered by freezing and thawing of the sample, and oftentimes cannot be determined at bedside) or can it be determined using control matrix from impaired patients that is spiked with the parent drug at concentrations corresponding to the observed mean values at peak and trough.

### **Calculation of PK parameters for unbound drug**

The draft guidance recommends that “the clearance and volume parameters should be expressed in terms of both unbound concentrations and total concentrations of drug in plasma and/or serum.”

**Recommendation:** We would appreciate input regarding FDA’s position about the acceptability of estimating PK parameter values for unbound drug by extrapolating measured free drug concentration at peak and trough to calculate the unbound fraction if the drug or metabolite is known to exhibit concentration independent binding. Further, if the unbound fraction is different between peak and trough concentrations, what approach should be used in calculating unbound AUC?

### **(E) Feasibility of Determining Dosing Recommendations for Hepatically Impaired Subjects using a Population PK Approach**

In this draft guidance, FDA has allowed for the use of a population PK screening approach to obtaining information on PK in patients with hepatic impairment (page 6). It was noted that these data would be sufficient to support a labeling claim that no dosage adjustment is required.

**Recommendation:** We would appreciate input from the FDA about the feasibility of using Population PK data for the determination of specific dosing recommendations (labeling) in Child’s A, Child’s B, and Child’s C patients.

## **(F) Labeling Section**

“...drug dosage should be reduced if the clearance of the study drug is *significantly impaired*...” (Page 8)

**Recommendation:** Clarification of what degree of reduction in clearance constitutes significant impairment will be useful.

## **(G) Clinical Pharmacology Section – Special Populations**

Guidance about labeling is not given for patients with severe impairment on pages 10-13.

**Recommendation:** FDA guidance on labeling scenarios for patients with severe impairment should be added to complete the discussion in this section.

Page 12 provides labeling statements for situations where extensive hepatic metabolism or elimination occurs:

“The influence of hepatic impairment on the pharmacokinetics of – has not been evaluated. Because there is in vitro and/or in vivo evidence of extensive hepatic contribution to the elimination of \_\_\_\_\_, hepatic impairment would be expected to have significant pharmacokinetic effects on \_\_\_\_\_.”

We appreciate the flexibility shown by the FDA in suggesting that it will be possible to create labeling statements for compounds extensively eliminated by hepatic impairment, even in the absence of data from a clinical study in patients with impaired hepatic function. However, it may be difficult to make specific recommendations regarding adjustment in the dose and/or frequency of administration without such data, even for drugs with a wide therapeutic index.

**Recommendation:** The FDA should consider clarifying under what conditions changes in treatment regimen can be proposed, even when data from a clinical study are not available.

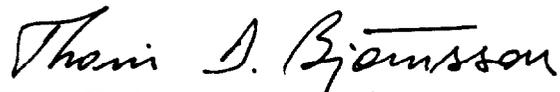
## **(H) Appendix – Addenda Necessary**

The draft guidance describes MEGX, and GSP but does not provide information about certain research quantitative liver function tests discussed in the background (e.g. antipyrine, or indocyanine green).

**Recommendation:** Please include specific information for the antipyrine and indocyanine green procedures

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Thorir D. Bjornsson, M.D., Ph.D.

Vice President,

Clinical Pharmacology and Experimental Medicine



Laurie Smaldone, M.D.

Senior Vice President,

Regulatory Science and Outcomes Research