
Guidance for Industry

Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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Comments on the document: Guidance for Industry- Pharmacokinetics in Patients With Impaired Liver Function: Study Design, Data analysis, and Impact on Dosing and Labeling

This guidance provides recommendations to sponsors planning to conduct studies to assess the influence of hepatic impairment on the pharmacokinetics, and where appropriate the pharmacodynamics of drugs or therapeutic biologics. This draft document is a first step in the right direction in establishing **minimum** responsibilities of the sponsor in terms of generating data to optimize drug therapy in patients with impaired liver function. However, there are a few concerns that we would like bring to the attention of those **concerned** individuals who drafted the guidance.

A. Use of a priori *in vivo* and *in vitro* data to aid in the design of studies in patients with impaired liver function.

Issue: The guidance suggests that correlation of the Child-Pugh score with various pharmacokinetic parameter estimates (including, oral clearance, volume of distribution, and half-life) serve as the major study endpoints. This suggestion, we believe, is an over generalization that does not take into account the wealth of information related to the hepatic elimination of a molecular entity that is typically obtained by the pharmaceutical companies prior to phase III studies. For the vast majority of new drugs, the following information will be known at the time a study is conducted in patients with hepatic impairment.

- The major route of elimination and extent of metabolism
- The degree of hepatic extraction of the new molecular entity
- The human enzymes involved in the formation of the major metabolite(s)

It is critical that this information be incorporated into the design of meaningful studies in patients with hepatic impairment.

Proposed Solution:

1. Relevant pharmacokinetic parameters obtained in patients with impaired hepatic function should be compared with a continuous measure of the hepatic function in addition to the categorical Child-Pugh score. The continuous variable used will depend on the known characteristics of the new molecular entity. For drugs that demonstrate a high hepatic extraction, measurement of effective hepatic blood flow using ICG or galactose would be recommended. For drugs with low hepatic extraction and metabolism involving multiple P450 isoforms, determination of the clearance of antipyrine is recommended. Finally, for drugs with specific primary metabolic pathways of elimination (eg. Protease inhibitors metabolized predominantly by CYP3A) correlation with the clearance of an isoform specific probe drug would be recommended.
2. For any drug whose metabolites are subsequently eliminated via the urine, it should be required that the urinary metabolites be measured and the formation clearance of that metabolic pathway be determined. This information is critical

C. When Studies are Important.

Issue: The guidance clearly states when a study is not important. However, it is not clear as to when a study is important. The guidance does not define “substantial” as it relates to a hepatically metabolized NME (page 3, paragraph 1, line 2).

Proposed Solution: It appears from the guidance that 20% hepatic metabolism is considered substantial. If this is the case, it needs to be stated categorically.

D. Protein Binding.

Issue: The guidance recommends measurement of unbound fraction at peak and trough concentrations. This is only acceptable when a drug exhibits concentration and time independent protein binding. Several currently marketed drugs demonstrate concentration and time dependent alterations in protein binding over the normal therapeutic range and would require a more detailed evaluation of protein binding.

Proposed Solution: The guidance should state that the use of peak and trough unbound fraction evaluations will only be acceptable for NME that demonstrate concentration and time independence over the normal therapeutic range. NME which demonstrate concentration and/or time dependent binding will require an evaluation of the unbound fraction in all samples to allow for an accurate determination of the area under the unbound drug concentration Vs time curve and the clearance of the unbound drug.

E. Other Issues.

Magnitude of Change in Parameters: Page 8, paragraph 2, line 3 of this document suggests that a dosage adjustment is needed only when a pharmacokinetic parameter is increased twofold or greater. This generalization would not be acceptable for a NME with a narrow therapeutic index. This statement should be removed and will need to be addressed specifically for each NME.

Route of Administration: The guidance does not mention issues related to route of administration. If a sponsor has a drug that is available in intravenous and oral formulations, it would be necessary for the NME to be evaluated using both formulations.

Clarification on Labeling: Page 12, paragraph 4, line 2 states that “Because less than 20% of the dose is excreted in the urine as unchanged drug and there is in vitro and in vivo evidence of extensive hepatic contribution to the elimination of _____, hepatic impairment would be expected to have significant pharmacokinetic effect on _____ population”.

The statement reads as though a study would not be required. This statement must be deleted as drugs with significant hepatic metabolism i.e. greater than 20%, must be evaluated in patients with hepatic impairment.

from several vantage points. First, the information about the formation clearance of the given metabolite can be coupled with the data from an *in vitro* expression system to provide isoform specific information about the elimination of a given molecular entity through a metabolic pathway. This information will also enhance the design of drug interaction studies that affect single CYP isoform. Second, the calculation of formation clearance is independent of the alterations in absorption that will contribute to the variability associated with the calculation of oral clearance. Increased variability due to changes in absorption may confound any correlation between Child-Pugh score and oral clearance; thereby, providing little information on the use of this compound in patients with hepatic failure.

B. Type of Hepatic Impairment and Control Group Considerations.

Issue #1: The guidance considers “liver disease” as one entity, without any distinction about the type of liver disease (i.e. cirrhosis vs. hepatitis; cholestatic vs. non-cholestatic). Including patients with liver disease of mixed etiologies in a limited sample of patients with moderate liver disease will likely increase data variability and may potentially confound study results. For example, *in vitro* data suggests that cholestatic and non-cholestatic liver diseases have different effects on various CYP enzymes. Although it is recognized that all types of liver disease can not be reasonably evaluated, the issue of disease etiology needs to be addressed.

Proposed Solution: Distinction of patients with cholestatic Vs non-cholestatic liver disease will be especially important for NME which demonstrate a high degree of biliary excretion. Therefore, it would be recommended that studies on NME’s ultimately excreted in the bile be conducted in patients with cholestatic liver disease. For NME which undergo hepatic metabolism and renal excretion of the metabolites the initial study should be carried out in a homogenous population (e.g. Hepatitis C or alcoholic cirrhosis etc.).

Issue #2: The guidance recommends (page 4, paragraph 4, line 4) the use of *patient populations* with normal hepatic function as a control group. Recruitment of such patients may not be practical in many cases. Even if patients can be recruited as controls, the data interpretation may be confounded by the use of several other drugs in this patient population, which may alter the hepatic metabolism of the NME. If the guidance implies that control group should consist of subjects matched for demographics of the patient with liver disease, that should be stated clearly.

Proposed Solution: Control subjects should consist of age, sex, weight, race and social habit (eg. smoking, alcohol consumption etc.) matched healthy volunteers to allow for the assessment of liver disease without the potential contribution of other medications or disease state.