Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2003
Clinical Pharmacology

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides recommendations to sponsors and applicants who plan to conduct studies to assess the influence of hepatic impairment on the pharmacokinetics (PK) and, where appropriate, the pharmacodynamics (PD) of a drug, including therapeutic biological products. This guidance discusses:

- When studies should and should not be conducted
- Recommended design and conduct of studies to characterize the effects of impaired hepatic function on the PK of a drug
- Inclusion criteria for patient populations to be studied
- Analysis, interpretation, and reporting of the results of the studies and description of the results in labeling

The guidance does not consider ways to assess the safety and efficacy of a drug to treat hepatic disease or how to assess whether a drug causes hepatotoxicity.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Hepatic Impairment Working Group in the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration, with contributions from the Center for Biologics Evaluation and Research (CBER).

II. BACKGROUND

The liver is involved in the clearance of many drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of unchanged drug or metabolites. Alterations of these excretory and metabolic activities by hepatic impairment can lead to drug accumulation or, less often, failure to form an active metabolite.

Many reports in the biomedical literature have documented that hepatic disease can alter the absorption and disposition of drugs (PK) as well as their efficacy and safety (PD). These reports have been based on studies in patients with common hepatic diseases, such as alcoholic liver disease and chronic infections with hepatitis viruses B and C, and less common diseases, such as acute hepatitis D or E, primary biliary cirrhosis, primary sclerosing cholangitis, and alpha$_1$-antitrypsin deficiency. Liver disease may also alter kidney function, which can lead to accumulation of a drug and its metabolites even when the liver is not primarily responsible for elimination. Liver disease may also alter PD effects (e.g., increased encephalopathy with certain drugs in patients with hepatic failure). The specific impact of any disease on hepatic function is often poorly described and highly variable, particularly with regard to effects on the PK and PD of a drug.

Measurements such as creatinine or creatinine clearance have been used successfully to adjust dosing regimens for drugs eliminated primarily by the kidneys. Similar measures of hepatic function have been sought using endogenous substances affected by the liver such as bilirubin and albumin, or functional measures such as prothrombin time, or the ability of the liver to eliminate marker substrates such as antipyrine (Figg et al., 1995), indocyanine green (ICG) (Figg et al., 1995), monoethylglycine-xylidide (MEGX) (Testa et al., 1997), and galactose (Tang and Hu 1992). Clinical variables have also been studied. These include ascites or encephalopathy, nutritional status, peripheral edema, and histologic evidence of fibrosis or combinations of variables such as the Child-Pugh classification for alcoholic cirrhosis and portal hypertension (Zakim and Boyer 1996; Pugh et al., 1973), the Mayo risk scores for primary biliary cirrhosis and primary sclerosing cholangitis (Dickson et al., 1989; Wiesner et al., 1989), and the Maddrey-Carithers discriminant function for acute alcoholic hepatitis (Maddrey et al., 1978; Carithers et al., 1989) (see Appendix). Despite extensive efforts, no single measure or group of measures has gained widespread clinical use to allow estimation in a given patient of how hepatic impairment will affect the PK and/or PD of a drug.

Even though clinically useful measures of hepatic function to predict drug PK and PD are not generally available, clinical studies in patients with hepatic impairment, usually performed during drug development, can provide information that may help guide initial dosing in patients. This information can be appropriately used with the understanding that careful observation and dose titration are critical to achieve the optimal dose in any given patient.

III. DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION

A. When Studies May Be Important

This guidance recommends a PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion (>20 percent of the absorbed drug) of the elimination of a parent drug or active metabolite. The guidance also recommends a hepatic impairment study even if the drug and/or active metabolite is eliminated to a lesser extent (<20 percent), if its labeling or literature sources suggest that it is a narrow therapeutic range drug.[2] If the metabolism of the drug is unknown and other information is lacking to suggest that hepatic elimination routes are minor, the Agency recommends that the drug be considered extensively metabolized.

B. When Studies May Not Be Important

For some drugs, hepatic functional impairment is not likely to alter PK sufficiently to require dosage adjustment. In such cases, a study to confirm the prediction is generally not important. The following drug properties may support this conclusion:

- The drug is excreted entirely via renal routes of elimination with no involvement of the liver.
- The drug is metabolized in the liver to a small extent (<20 percent), and the therapeutic range of the drug is wide, so that modest impairment of hepatic clearance will not lead to toxicity of the drug directly or by increasing its interaction with other drugs.
- The drug is gaseous or volatile, and the drug and its active metabolites are primarily eliminated via the lungs.

For drugs intended only for single-dose administration, a hepatic impairment study will generally not be useful, unless clinical concerns suggest otherwise.

IV. STUDY CONSIDERATIONS

The following sections of the guidance focus on a basic *full* study design (Section A), a *reduced* study design (Section B), and a population PK approach (Section C).

A Basic *Full* Study Design

To develop specific dosing recommendations across the entire spectrum of hepatic impairment, a study should be carried out in patients in the three Child-Pugh categories, mild, moderate and severe, as well as controls. For this study design to provide evaluable

[2] The *therapeutic range (TR)* can be derived from the concentration- or dose-response data existing in the safety and efficacy database preapproval or from data obtained postapproval.

data, at least six subjects in each arm should be evaluated and all other considerations set forth in section B should be taken into account.

B. *Reduced* Study Design

1. Study Participants

An FDA survey of 57 PK studies in patients with hepatic impairment in new drug applications submitted between 1995 and 1998 revealed that 55 percent used the Child-Pugh scale to assess hepatic impairment. Of the 57 studies surveyed, 19 estimated oral drug clearance in normals and in patients in more than one Child-Pugh category (i.e., mild, moderate, or severe). Of those 19 studies, 17 demonstrated a negative correlation (r^2 between 0.5 to 1.0) between oral drug clearance and hepatic impairment, and 16 showed impaired hepatic metabolism in the patients in the moderate Child-Pugh category.

Based on these data, this guidance recommends that the Child-Pugh classification be used to categorize the degree of hepatic impairment in patients, just as serum creatinine or creatinine clearance is used to categorize varying degrees of renal impairment. In patients evaluated for this purpose, it is important that impaired hepatic function — not some other underlying disease — be the cause of alterations in the Child-Pugh components (bilirubin, albumin, prothrombin, encephalopathy and ascities). For example, in patients with metastatic cancer, hypoalbuminemia, encephalopathy, and ascites may be related to cancer cachexia or cancer metastatic to the brain or peritoneal surfaces rather than impaired hepatic function. Other approaches to assess varying degrees of hepatic impairment may be appropriate, but a Child-Pugh categorization should still be included for each patient.

Also, based on the above data, a study design involving control subjects and patients with a Child-Pugh category of moderate would generally be appropriate. In that case, the findings in the moderate category would be applied to patients with a mild Child-Pugh category, and dosing in the severe category would generally be contraindicated (see the Labeling section for details).

The primary purpose of this guidance is to help sponsors and applicants determine, based on the behavior of the drug in patients with normal liver function, whether the PK and/or PD of a drug and its active metabolites are altered in patients with hepatic impairment to the extent that an adjustment to the dosage would be indicated. For this reason, the control group should be derived from the intended patient population (with apparently normal hepatic function), not from young, healthy volunteers. To the extent possible, the control group should be similar to patients with respect to age, weight, and sex. Depending on the drug, consideration is also recommended of other factors with significant potential to affect the PK of a drug to be studied (e.g., diet, smoking, alcohol intake, concomitant medications, ethnicity). If concomitant medications are used in the patients being studied, a careful assessment of their influence on PK or PD should be made at the time of data analysis. For drugs whose metabolism is mediated by enzymes

known to exhibit genetic polymorphism (e.g., CYP450, 2D6, or 2C19), the sponsor should take into consideration the metabolic status of the enrolled subjects when analyzing the results of the study. In addition to standard clinical tests performed prior to entry, sponsors and applicants are urged to perform assessments of hepatic blood flow and/or intrinsic clearance using appropriate markers.

A sufficient number of subjects should be enrolled in the study to provide evaluable data from at least eight subjects in the control and the moderate impairment arms.

2. Drug Administration

A clinical study to investigate the effects of hepatic impairment on drug disposition can be designed, depending on circumstances, as a single-dose or multiple-dose study with PK assessment of the parent drug and any active metabolite(s). In a multiple-dose study, PK assessment is appropriately carried out at steady state. A single-dose study may be satisfactory for cases where prior evidence indicates that multiple-dose PK is accurately predicted by single-dose data for both parent drug and active metabolites. This would be the case when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the patients to be studied. A multiple-dose study is desirable when the drug or an active metabolite is known to exhibit nonlinear or time-dependent PK. Although the planned clinical dose is generally recommended as the appropriate dose to be used in the study, a reduced dose may be appropriate in patients with hepatic impairment if concern exists about drug toxicity in patients with increased blood levels. If more than one route of administration is proposed for a drug, the study should use the route that provides the maximum information regarding the impact of hepatic impairment on the candidate drug's elimination.

3. Sample Collection and Analysis

The blood sampling duration should be adequate to determine the terminal half-life of the drug and its active metabolite(s), with the expectation that these times may be extended in the patient compared to the control population. For drugs that are highly extracted by the liver (extraction ratio > 0.7) and that are extensively bound to plasma proteins (fraction unbound < 10 percent), the Agency recommends that the unbound fraction be determined at least at trough and maximum plasma concentration. The clearance and volume parameters are appropriately expressed in terms of both unbound and total concentrations of drug in plasma/serum/blood. To allow for analysis of the parent drug and its active metabolite(s), analytical methods should exhibit sufficient sensitivity and specificity. For drugs with stereochemical properties, stereoselectivity in drug metabolism and protein binding of enantiomers merit consideration (FDA 1992).

C. Population PK Approach

Population PK screening in phases 2 and 3 can be useful in assessing the impact of altered hepatic function (as a co-variate) on PK if (1) these patients are not excluded from phase 2 and 3 trials and (2) there is enough PK information collected about patients to characterize them reasonably well. If a population PK approach is used, patients in phase 2 and 3 studies should be assessed for encephalopathy, ascites, serum bilirubin, serum albumin, and prothrombin time (components of the Child-Pugh score) or a similar group of measures of hepatic function. A population PK study should include the following features:

- Preplanned analysis of the effect of hepatic impairment
- Appropriate evaluation of the severity of liver disease
- A sufficient number of patients and a sufficient representation of the entire range of hepatic function to allow the study to detect PK differences large enough to warrant dosage adjustment
- Measurement of unbound concentrations of the drug when appropriate
- Measurement of parent drug and active metabolite(s)

Such features are important if the sponsor intends to use the results to support a conclusion that no dosage adjustment is required for patients with impaired hepatic function. Sponsors and applicants are referred to the FDA guidance for industry *Population Pharmacokinetics* (FDA 1999) for more detailed information about the design and execution of population PK studies,

D. Pharmacodynamic Assessments

Pharmacodynamic assessments may be useful in studies designed to assess the effect of altered liver function, especially if concentration-response data are not available or if there is a concern that altered hepatic function may alter PD response. The Agency recommends that the selection of PD endpoints be discussed with appropriate FDA review staff and that they be based on the pharmacologic characteristics of the drug and its active metabolites.

V. DATA ANALYSIS

The primary intent of the data analysis is to assess the effect of hepatic impairment on the PK of the drug and its active metabolites and, if possible, to relate a specific measure of hepatic function or group of functions (e.g., Child-Pugh) to a relevant PK measure or parameter such as the area under the plasma concentration curve (AUC). From this information, dosage recommendations for patients with impaired hepatic function can be developed.

A. Parameter Estimation

Plasma concentration data (and urine concentration data, if collected) should be analyzed to estimate measures or parameters describing the PK of the drug and its active metabolite(s) (e.g., AUC, peak concentration, (C_{max}), apparent clearance (CL/F), renal and nonrenal clearance (CL_R and CL_{NR}), apparent volume of distribution (Vd_z or Vd_{ss}), terminal half-life ($t_{1/2}$)). Where relevant, measures or parameters can be expressed in terms of unbound concentrations (e.g., apparent clearance relative to the unbound drug concentration (Clu/F=Dose/AUCu, where the subscript "u" indicates unbound drug)). Noncompartmental and/or compartmental modeling approaches to parameter estimates can be employed.

B. Relationship Between Measures of Hepatic Function and PK

In contrast to approaches relating measures of renal impairment to drug disposition, past experience indicates that it has been difficult to develop a measure or group of measures of hepatic function that predict alterations in drug PK. Nonetheless, relationships between hepatic functional abnormalities (e.g., hepatic blood flow, serum albumin concentration, prothrombin time, or overall impairment scores such as Child-Pugh), and selected pharmacokinetic parameters (e.g., total body clearance, oral clearance, apparent volume of distribution, unbound clearance or dose-normalized area under the unbound concentration-time curve) should be sought using linear and nonlinear models. A regression approach for continuous variables describing hepatic impairment and PK parameters is appropriate, with the understanding that some correlations will rely on categorical variables (e.g., Child-Pugh). Typically, modeling results would include parameter estimates of the chosen model and measures of their precision (standard errors or confidence intervals). Prediction error estimates are also desirable to assess appropriateness of the model.

C. Development of Dosing Recommendations

The principal objective of a hepatic impairment study is to develop dosing recommendations so that patients and practitioners can alter dose and dosing interval appropriately in the presence of hepatic disease, again noting that subsequent careful titration and observation are critical in this vulnerable population. When applicable, it is also important to point out in dosing recommendations that hepatic impairment does ***not*** alter a drug's PK. To reach this conclusion, a confidence interval approach, rather than a significance test, is preferred.

A general approach in developing dosage recommendations is appropriately based on the following considerations:

- If the effect of hepatic impairment on the PK of the drug is obvious (e.g., two-fold or greater increase in AUC), dosage adjustments should be recommended in labeling. It should be noted that for prodrugs (i.e., drugs with activity predominantly due to hepatically generated metabolite), it is possible that the dose would be increased, or the dosing interval shortened, in hepatically impaired patients.

- A conclusion that there is ***no effect*** (really, no clinically important effect) of hepatic impairment on the drug's PK, would usually be supported by the establishment of one of the following: (1) delineation of *no effect* boundaries, prior to the conduct of the studies, based on information available for the investigational drug (e.g., dose- and/or concentration-response studies), or (2) in the absence of other information to determine a different equivalence interval, the employment of a standard 90 percent confidence interval of 80-125 percent for AUC and C_{max}. FDA recognizes that documentation that a PK parameter remains within an 80-125 percent *no effect* boundary would be very difficult given the small numbers of subjects usually entered into hepatic impairment studies. If a wider boundary can be supported clinically, however, it may be possible to conclude that there is no need for dose adjustment.

VI. LABELING

Labeling should reflect the data pertaining to the effect of hepatic impairment on a PK and PD of a drug (if known). Although the many permutations of intrinsic drug characteristics and the effect of hepatic impairment on drug performance preclude a simple specification of the labeling for such drugs, in general drug dosage should be reduced in the relevant population (Child-Pugh) for which significantly impaired clearance is shown. Depending on the drug's use and therapeutic range, and the size of the effect on clearance, the drug may be contraindicated in severe (Child-Pugh) hepatic impairment or used with great caution. Conversely, if the results show no significant impairment of drug clearance in the moderate group, the drug can be administered in mild and moderate hepatic impairment without any dose modification. Labeling would generally indicate caution for severe hepatic impairment if the drug has significant hepatic clearance, and if there are no data to support a lesser labeling restriction.

If a study is not conducted for the reasons listed in Section III.B, labeling should indicate that the impact of hepatic impairment was not studied and that effects requiring a dosage adjustment are unlikely for the proposed drug. More detailed recommendations for labeling statements are provided in the following sections.

A. Clinical Pharmacology

1. Pharmacokinetics Section

Information in this section of the labeling should include:

- The mechanism of hepatic elimination (e.g., enzyme pathways, glucuronidation, biliary excretion)
- The percent of drug that is eliminated by these mechanisms (e.g., metabolism, biliary excretion)
- The disposition of active metabolites in patients with impaired hepatic function, if applicable
- The effects of hepatic impairment on protein binding of parent drug and metabolites, if applicable

- If applicable, a description of the effects of impaired hepatic function on stereospecific disposition of enantiomers of a racemic drug product if there is evidence of differential stereoisomeric activity or toxicity

2. Special Populations Section

Based on studies performed in accordance with recommendations in this guidance or an acceptable alternative, information in this section of the labeling should include:

- A brief description of the pharmacokinetic changes found in patients with hepatic impairment
- Discussion of any issues of altered PD and dosing adjustments required for patients with hepatic impairment
- A reference to the WARNINGS/PRECAUTIONS, CONTRAINDICATION and DOSAGE AND ADMINISTRATION sections.

The following text provides examples of appropriate wording for this section of the labeling.

a. If studies show no effect of altered hepatic function

The simplest situation involves drugs for which studies of impaired hepatic function have been conducted and little or no effect on PK or PD was noted.

> *In a study comparing [X] patients with moderate (as indicated by the Child-Pugh method) hepatic impairment to [X] controls, the single/multiple dose PK/PD disposition of _____ was not altered in patients with hepatic impairment. No dosing adjustment is required in patients with mild and moderate hepatic impairment.*

b. If studies show an effect of altered hepatic function

For drugs in which PK or PD is influenced by hepatic impairment, the following statement can be modified as appropriate and in accordance with what is known about the drug (e.g., racemate with different activity of stereoisomers, active or toxic metabolite) and from the studies performed in accordance with this guidance.

> *The disposition of _____ was compared in patients with hepatic impairment and subjects with normal hepatic function. Total body clearance of [unbound, if applicable] _____/metabolite was reduced by ___% in patients with moderate (as indicated by the Child-Pugh method) hepatic impairment. The half-life of _____/metabolite is prolonged by ____ in patients with moderate hepatic impairment. Protein binding of _____/metabolite [is/is not] affected by impaired hepatic function. The drug/metabolite accumulates to the extent of*

> *____ in patients with impaired hepatic function on chronic administration. The dosage should be reduced in patients with mild and moderate hepatic impairment receiving _____. _____ should be [contraindicated/used with great caution] in severe hepatic impairment (see WARNINGS/PRECAUTIONS, CONTRAINDICATION and DOSAGE AND ADMINISTRATION).*

c. If no studies of a population with altered hepatic function exist

In cases where no hepatically impaired patient population has been investigated, as the basis for labeling claims, the following labeling language is recommended:

Option 1: For no hepatic contribution to the elimination of the compound

> *The influence of hepatic impairment on the pharmacokinetics of_____ has not been evaluated. Because greater than 90% of the dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on _____elimination.*

Option 2: For limited (<20 percent) hepatic elimination

Wide Therapeutic Range

> *The influence of hepatic impairment on the pharmacokinetics of_____ has not been evaluated. Because greater than 80% of the dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to lead to unsafe systemic exposure of _____.*

Narrow Therapeutic Range

> *The influence of hepatic impairment on the pharmacokinetics of_____ has not been evaluated. Because the usual doses of the drug are close to doses that can cause adverse effects, and there is in-vitro or in-vivo evidence of hepatic contribution to the elimination of_____, hepatic impairment could lead to an increased exposure and possibly an increase in adverse effects. Patients with impaired liver function may require reduced doses of _____or longer dosing intervals. If _____ is used, close monitoring of patients with impaired liver function is important (see WARNINGS/PRECAUTIONS, CONTRAINDICATION and DOSAGE AND ADMINISTRATION).*

Option 3: For extensive (> 20 Percent) hepatic elimination

Wide Therapeutic Range

The influence of hepatic impairment on the pharmacokinetics of____ has not been evaluated. Because there is in-vitro or in-vivo evidence of extensive hepatic contribution to the elimination of _____, hepatic impairment would be expected to have significant effects on the pharmacokinetics of _____. Caution should be exercised during the use of ____ in this patient population. Patients with impaired liver function may require reduced doses of _____ or longer dosing intervals (see WARNINGS/PRECAUTIONS, CONTRAINDICATION and DOSAGE AND ADMINISTRATION).

Narrow Therapeutic Range

The influence of hepatic impairment on the pharmacokinetics of____ has not been evaluated. Because there is in-vitro or in-vivo evidence of extensive hepatic contribution to the elimination of _____, hepatic impairment would be expected to have significant effects on pharmacokinetics of _____. ____ should be avoided or used with great caution in this patient population (see WARNINGS/PRECAUTIONS, CONTRAINDICATION and DOSAGE AND ADMINISTRATION).

Option 4: For unknown hepatic elimination

In these circumstances, consider the compound as extensively metabolized and use the above format.

B. Precautions/Warnings

Use in Patients with Impaired Hepatic Function: If the effects of hepatic impairment result in clinically important changes in drug PK or PD, this information should be included in the PRECAUTIONS section of the labeling with reference to DOSAGE AND ADMINISTRATION. If there is no information on the PK in patients with impaired hepatic function, but the drug is known to have a narrow therapeutic range, a statement in the PRECAUTIONS, WARNINGS or CONTRAINDICATIONS sections of the labeling should be included as appropriate.

C. Dosage and Administration:

As appropriate, the following statements are recommended:

The influence of impaired hepatic function on _____ pharmacokinetics or pharmacodynamics (if known) is sufficiently small that no dosing adjustment is required.

For cases in which impaired hepatic function requires dosing adjustments, the appropriate information should be included.

Special consideration should be given to combination drug products. It is reasonable to recommend dosing adjustment according to the degree of hepatic impairment if there is sufficient information to indicate that the pharmacokinetics of the individual components are similarly affected by impaired hepatic function. In situations for which this does not apply, the following statement should be included:

> *Because the doses of this fixed combination product cannot be individually titrated and impaired hepatic function results in a reduced clearance of component A to a much greater extent than component B, the combination product should generally be avoided in patients with impaired hepatic function (see WARNINGS or PRECAUTIONS, as appropriate).*

In some cases, where various ratios of the combination product are available, it may be possible to direct physicians to a combination with less of the hepatically cleared component.

REFERENCES

Carithers RL, Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon H, Maddrey WC, Methyl-prednisolone therapy in patients with severe alcoholic hepatitis, *Ann Intern Med* 1989; 110:685-90.

Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A, Prognosis in primary biliary cirrhosis: model for decision making, *Hepatology* 1989; 10:1-7.

FDA, *Policy Statement for the Development of New Stereoisomeric Drugs*, May 1992.

FDA, *Population Pharmacokinetics*, February 1999.

Figg WD, Dukes GE, Lesesne HR, Carson SW, Songer SS, Pritchard JF, Hermann DJ, Powell JR, and Hak LJ, Comparison of quantitative methods to assess hepatic function: Pugh's classification, indocyanine green, antipyrine, and dextromethorphan, *Pharmacother* 15:693-700, 1995.

Maddrey WC, Boitnott JK, Bedine MS, Weber FLJr, Mezey E, White RI, Corticosteroid therapy of alcoholic hepatitis, *Gastroenterology* 1978; 75:193-9.

Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R, Transection of the oesophagus for bleeding oesophageal varices, *Brit J Surg* 1973; 60:646-9.

Tang H-S, Hu OY-P, Assessment of liver function using a novel galactose single point method, *Digestion* 1992; 52:222-31.

Testa R, Caglieris S, Risso D, et al., Monoethylglycinexylidide formation measurement as a hepatic function test to assess severity of chronic liver disease, *Am J Gastroenterol* 1997; 92:2268-73.

Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, et al., Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis, *Hepatology* 1989; 10:430-6.

Zakim D and Boyer TD, Hepatology, *A Textbook of Liver Disease*, W. B. Saunders Company, Philadelphia, 1996.

APPENDIX: ASSESSMENT OF LIVER FUNCTION.

1. Child-Pugh system

	Points Scored for Observed Findings		
	1	2	3
Encephalopathy grade*	none	1 or 2	3 or 4
Ascites	absent	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged	<4	4 to 6	>6

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Assessment as good operative risk (A or mild) if 5 or 6 points; moderate risk (B or moderate) if 7 to 9 points; and poor operative risk (C or severe) if 10 to 15 points. (Developed for surgical evaluation of alcoholic cirrhotics.)

2. Maddrey discriminant function (df)

df = 4.6 x (prothrombin time, in seconds) + serum total bilirubin, mg/dL

Interpretation of the df values in patients with acute alcoholic hepatitis was that the disease was not severe if df <54, was severe if 55 to 92, and probably lethal if 93 or more and untreated.

The df was modified in a later study by Carithers, et al., (1989) to use the prolongation of prothrombin time above normal control values and to divide the serum bilirubin by 17.1 to give mmol/L. Patients with modified df values of 32 or more were entered into a study of methylprednisolone treatment, corresponding to Maddrey df values of approximately 106.

3. Mayo Survival Model for Primary Biliary Cirrhosis

This model, based on Cox proportional hazards regression analyses for factors predicting death, used the five most influential variables in a complex formula to calculate estimate survival time, S(t), in terms of mortality risk, R:

$$S(t), \text{survival probability for t years} = \{S_0(t)\}^{\exp(R-5.07)}, \text{ where}$$
$$R = 0.871 \ln (B) + 2.53 \ln (A) + 0.039 (Y) + 0.859 (E) + 2.38 \ln (PT).$$

[B=bilirubin, mg/dL; A=albumin, g/dL; Y=age in years; E=edema; PT=prothrombin time, sec]

$S_0(t)$ is taken from a table of observed survivals for R =5.07, the mean value of risk score found in the 418 patients observed:

t, years	1	2	3	4	5	6	7
$S_0(t)$	0.970	0.941	0.883	0.833	0.774	0.721	0.651

Later the same year, another model was developed for 174 patients with primary sclerosing cholangitis (PSC) by Wiesner and colleagues at the same institution, but the regression analysis identified blood hemoglobin (Hb, g/dL, below 12 g/dL), inflammatory bowel disease (IBD: 1 if yes, 0 if no), and the histologic stage of hepatic fibrosis (S, 0 to 4) as important, in addition to age and serum bilirubin (up to 10 mg/dL used if observed value higher):

$$R = 0.85 \ln (B) + 0.06 (Y) - 4.39 \ln (Hb) + 1.59 (IBD) + 0.51 S$$

4. Antipyrine

In contrast to the flow dependent indocyanine green (ICG), antipyrine has a low hepatic extraction ratio (2 percent) (Figg et al., 1995). It is almost completely oxidized by various hepatic enzymes (2-hydroxylation and 1-N-demethylation) and is limited by metabolic capacity of the intrinsic enzyme activity and not necessarily by hepatic blood flow or hepatic uptake. It has been used extensively as a general marker for the functional ability of the cytochrome P-450 oxidative pathway and is affected by a wide range of liver diseases (e.g., chronic liver disease, hepatitis, and cirrhosis). Antipyrine is effective in identifying moderate and severe hepatic impairment, but its clearance does not change in mild liver disease. Antipyrine clearance was found to significantly correlate with Child-Pugh's classification (r=0.67, p=0.0003).

5. Indocyanine Green (ICG)

A widely used marker of hepatic blood flow and hepatic uptake is ICG (Figg et al., 1995). ICG is highly extracted by the liver (70-90 percent), is not recovered in urine, is 95 percent bound to circulating albumin, and is cleared by hepatic uptake, conjugation, and excretion into the bile. Hepatic blood flow as assessed by clearance of ICG is highly correlated with direct measurement using electromagnetic flow meters. At standard doses, its clearance follows first order kinetics. ICG clearance is reduced in all forms of chronic liver disease. Elimination is particularly impaired in alcoholic and biliary cirrhosis. The percentage reduction found in patients with established cirrhosis varies from 35-94 percent of that in healthy controls. ICG clearance was found to correlate significantly with Child-Pugh's classification (r=0.86, p=0.0001).

6. Monoethylglycinexylidide (MEGX)

This compound is the main metabolite of lidocaine, produced by oxidative N-de-ethylation by the hepatic CYP 3A enzyme system. It is measured at 15, 30, or 60 minutes after an intravenous

infusion over 2 minutes of 1 mg/kg of lidocaine, and correlates well with Child-Pugh scores (Testa et al., 1997).

7. Galactose Single Point (GSP) Method

A simplification (Tang and Hu 1992) of the older, more tedious galactose elimination constant (GEC) developed by Tygstrup in 1963 has been validated in patients with chronic hepatitis and cirrhosis graded by the Child-Pugh scale and GEC. The test is done by intravenously infusing 0.5 g/kg of galactose and measuring serum galactose concentration enzymatically at 60 minutes later. Elevated blood galactose correlates sensitively with hepatic dysfunction. There is some evidence that the GSP test can be used to define clearance of both highly metabolized drugs and drugs that are hepatically excreted but not metabolized.