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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

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

September 2026
Clinical Pharmacology

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Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosage Guidance for Industry[1]

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I. INTRODUCTION

This guidance assists sponsors in the design and analysis of studies that assess the influence of impaired hepatic function, herein referred to as hepatic impairment (HI), on the pharmacokinetics and, where appropriate, the pharmacodynamics of a drug.[2,3]

This guidance provides recommendations on the following topics:

- When studies to assess the influence of HI on the pharmacokinetics or pharmacodynamics of a drug should be conducted and when they may not be warranted
- Design and conduct of studies to characterize the effects of HI on the pharmacokinetics of a drug, including the population pharmacokinetic (popPK) approach
- Data analysis and interpretation of these study results, as well as the evaluation of relationships between measures of hepatic function and pharmacokinetic and/or pharmacodynamic parameters

[1] This guidance has been prepared by the Office of Clinical Pharmacology in the Office of Translational Sciences, with support from the Division of Hepatology and Nutrition, Office of New Drugs, both in the Center for Drug Evaluation and Research (CDER) at the FDA.

[2] For the purposes of this guidance, references to *drugs* and *drug products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and therapeutic peptides and proteins licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) that are regulated as drugs. Hereafter, the term *drug* or *drugs* will be used to refer to all such products unless otherwise specified.

[3] In the notice announcing the availability of this draft guidance, FDA also withdrew the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003), which formerly provided FDA's thinking on studies to assess the influence of HI on the pharmacokinetics or pharmacodynamics of a drug and recommendations to include HI information in labeling.

In general, FDA's guidance documents 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.

II. BACKGROUND

The liver is a major organ involved in the elimination of drugs through metabolism and/or biliary excretion of unchanged drugs or their metabolites. Liver disease can change these metabolic and excretory pathways by impacting drug metabolizing enzymes and transporters.[4,5] In addition, the absorption and distribution of drugs can also be affected by liver disease. The presence and magnitude of portal hypertension in patients with cirrhosis can further affect a drug's pharmacokinetics to varying degrees because of alterations in hepatic arterial and portal blood flow as well as intra- and extra-hepatic shunting. Portal hypertension can also affect systemic circulation, leading to changes in the volume of distribution of a drug. In patients with advanced cirrhosis, protein binding can be affected due to associated hypoalbuminemia. Transporter function can also be affected in patients with liver disease. In summary, liver disease can lead to changes in a drug's pharmacokinetics, to a degree necessitating different recommendations for use of the drug (e.g., a different recommended dosage in patients with HI).

Although therapeutic peptides and proteins are not generally considered to be substrates of drug transporters or drug metabolizing enzymes of the cytochrome P450 family or, their pharmacokinetics can be altered by other mechanisms in patients with HI. Altered pharmacokinetics of monoclonal antibodies and antibody-drug conjugates has been reported in patients with HI and should be considered during drug development.[6]

Liver disease can also alter the pharmacodynamic effects of a drug, potentially affecting safety (e.g., increased sedation if patients with hepatic encephalopathy are treated with benzodiazepines; impaired synthesis of coagulation factors in patients with cirrhosis may increase the bleeding risk of direct-acting oral anticoagulants). Liver disease can also alter kidney function (e.g., hepatorenal syndrome), potentially leading to changes in the pharmacokinetics of a drug and its metabolites even when the liver is not primarily responsible for their elimination. The specific impact of various phenotypes of liver disease (e.g., hepatocellular vs. cholestatic, acute vs. chronic) on hepatic function is still not completely

[4] Verbeeck R, 2008, Pharmacokinetics and Dosage Adjustment in Patients with Hepatic Dysfunction, Eur J Clin Pharmacol, 64:1147–1161.

[5] Ali I, JR Slizgi, JD Kaullen, M Ivanovic, M Niemi, PW Stewart, AS Barritt, and KLR Brouwer, 2018, Transporter-Mediated Alterations in Patients with NASH Increase Systemic and Hepatic Exposure to an OATP and MRP2 Substrate, Clin Pharm Ther, 104(4):749–756.

[6] Sun Q, S Seo, S Zvada, C Liu, and K Reynolds, 2020, Does Hepatic Impairment Affect the Exposure of Monoclonal Antibodies?, Clin Pharm Ther, 107(5):1256–1262.

understood, making it challenging to predict the effects of different phenotypes of liver disease on the pharmacokinetics and pharmacodynamics of a drug.

Patients with HI have often been excluded from clinical trials, even when they are part of the intended target population. Characterizing the impact of HI on pharmacokinetics during early clinical drug development and employing modeling and simulation strategies, where feasible, can facilitate inclusion of patients with HI in clinical trials. This approach would facilitate the applicability of trial findings to patients with HI who are likely to use the drug upon approval.[7,8]

Based on the above considerations, it is important to characterize the impact of HI on the pharmacokinetics and, where appropriate, on the pharmacodynamics of a drug during drug development to help determine if risk mitigation is needed with the use of the drug in patients with HI (e.g., a modified dosage, increased monitoring of adverse events).

III. DECIDING WHETHER TO CONDUCT A DEDICATED PHARMACOKINETIC STUDY IN PATIENTS WITH HEPATIC IMPAIRMENT

A. When a Dedicated Pharmacokinetic Study Should be Conducted

A pharmacokinetic study in subjects with HI is recommended if any of the following conditions are met:

- Hepatic metabolism and/or excretion accounts for >30 percent of the elimination of absorbed parent drug or active metabolites.[9]
- Minimal drug concentration changes may lead to clinically significant differences in safety or effectiveness.
- The elimination pathways of the drug are not adequately characterized.
- The drug is intended to treat patients with liver disease.
- The drug is likely to be used in patients with HI.

[7] See the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] See the guidance for industry *Enhancing Participation in Clinical Trials — Eligibility Criteria, Enrollment Practices, and Trial Designs* (December 2025).

[9] Active metabolites are moieties possessing either significant therapeutic or adverse activity.

B. When a Dedicated Pharmacokinetic Study May Not Be Warranted

If HI is not likely to alter the pharmacokinetics of a drug sufficiently to necessitate a different recommended dosage in patients with HI, a dedicated pharmacokinetic HI study is generally not warranted, unless clinical concerns suggest otherwise. The following drug properties could support this conclusion when the drug is:

- Metabolized and/or excreted by the liver to a small extent (< 30 percent of the absorbed drug in humans) and minimal drug concentration changes do not lead to clinically significant differences in safety or effectiveness.
- Excreted entirely via the renal route with no involvement of the liver.
- Intended only for single administration.
- Locally acting with limited or no systemic exposure.
- Gaseous or volatile, and the drug and its active metabolites are primarily eliminated via the lungs.

C. Timing of the Hepatic Impairment Study

The effect of HI should be assessed early in drug development to adequately guide trial eligibility and identify a recommended dosage for patients with HI.

In the case of orphan drugs, where the population with the disease is fewer than 200,000, sponsors should reach out to the appropriate FDA review division early during drug development to discuss the timing and characterization of the pharmacokinetics of a drug in subjects with HI.

IV. STUDY DESIGN CONSIDERATIONS

The primary purpose of the dedicated HI study is to characterize the impact of HI on the pharmacokinetics of the drug and determine whether the extent of the changes in the pharmacokinetics, and where appropriate the pharmacodynamics, of the drug warrants different conditions of use in patients with HI (e.g., avoiding use, modified recommended dosage, increased monitoring for adverse reactions).

This section describes the considerations for the design of a dedicated HI study.

A. Assessment of Hepatic Function

FDA recommends using the Child-Pugh (CP) classification to categorize the degree of HI in subjects with cirrhosis due to chronic liver disease. In subjects with cancer, sponsors can use the National Cancer Institute (NCI) Organ Dysfunction Working Group criteria (NCI Criteria) to categorize the degree of HI, except for subjects with hepatobiliary cancers. For subjects with hepatobiliary cancers in which cirrhosis may be the key risk factor, FDA recommends using the

CP classification unless known safety considerations preclude use of the drug in subjects with advanced cirrhosis. FDA does not recommend the use of the NCI Criteria to assess hepatic function for non-cancer patients.

Other approaches may be considered to identify patients with HI for a given indication (See IV.A. 3. Other Assessments of Hepatic Function). FDA recommends that sponsors consult with the appropriate FDA review division if they plan to use a hepatic classification system other than CP in subjects without cancer or the NCI Criteria in subjects with cancer (except hepatobiliary cancers).

1. Child-Pugh Classification

The CP[10] classification system, originally developed for patients with cirrhosis undergoing portocaval shunt surgery, is based on points contributed by five components, as shown in Table 1. HI is classified as *mild*, *moderate*, or *severe,* which corresponds to CP scores of 5-6 (CP group A), 7-9 (CP group B), and 10-15 (CP group C), respectively. Despite some limitations (e.g., subjective assessment of ascites), the CP classification continues to be a useful marker of liver function and is generally accepted to predict changes in pharmacokinetics for the purposes of drug development.

Table 1. Child-Pugh Classification

	Points Scored for Observed Findings		
	1	**2**	**3**
Encephalopathy grade	none	1 or 2	3 or 4
Ascites	absent	slight	moderate
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, seconds prolonged or INR*	<4 < 1.7	4 to 6 1.7 to 2.3	>6 > 2.3

* INR: international normalized ratio

The study report should provide both the total CP score and the values of each of the five components as well as a clear description of how ascites and hepatic encephalopathy severity or grade were determined, including the condition of assessment during scoring (e.g., ascites severity assessment with or without diuretic use).

When assessing CP score, investigators should ensure that changes in these components of the score are due to an underlying hepatic disease or worsening of hepatic function. Elevations in total bilirubin, international normalized ratio (INR), as well as reductions in albumin could occur because of co-morbid conditions unrelated to worsening hepatic function. For example, Vitamin K deficiency or anti-coagulant drugs may increase INR, Gilbert's syndrome may increase total bilirubin via unconjugated bilirubin, and intravenous fluid administration may dilute serum

[10] Pugh RNH, IM Murray-Lyon, JL Dawson, MC Pietroni, and R Williams, 1973, Transection of the Oesophagus for Bleeding Oesophageal Varices, Brit J Surg. 60:646–649.

albumin. Further, determining a CP score during or shortly after an acute event (e.g., alcohol recidivism, gastrointestinal bleed, surgery, transfusions, infections, flare of underlying liver disease) is not recommended because it may produce a higher score that may not reflect baseline drug metabolic capacity.

2. NCI Criteria

The NCI Criteria uses total bilirubin and aspartate aminotransferase to assess HI and commonly stratify patients into four groups or cohorts (A: normal, B: mild, C: moderate, D: severe) according to their liver test results (see Table 2).[11]

Table 2. NCI Criteria

Group Hepatic Function	Group A Normal	Group B Mild	Group C Moderate	Group D Severe
Total Bilirubin	≤ULN*	B1: ≤ULN B2: >1x-1.5x ULN	>1.5x-3x ULN	>3x ULN
Aspartate aminotransferase	≤ULN*	B1: >ULN B2: Any	Any	Any

* ULN: upper limit of the normal range

3. Other Assessments of Hepatic Function

Other scoring systems using laboratory tests to assess the severity of liver disease exist, e.g., the Model of End-Stage Liver Disease (MELD) score and the Albumin-Bilirubin (ALBI) score. However, these scoring systems have not been sufficiently characterized with respect to their ability to predict changes in pharmacokinetics to support their use in lieu of the CP score. When using the CP classification, MELD scores can be useful for further stratification of disease severity within CP groups B and C. Generally, when alternative scores are used, the CP classification should also be assessed, and results should be reported for all classification methods. FDA encourages assessment of other relevant markers to explore correlation with pharmacokinetic change.

Exogenous marker or probe drug tests may be used as exploratory tools for assessing hepatic drug clearance and possibly support an alternative dosage in patients with HI (compared to those with normal hepatic function) in conjunction with use of appropriate hepatic classification.

B. Dedicated Pharmacokinetic Study Design

1. Study Subjects

The sponsor should conduct a study in subjects with mild, moderate, and severe HI, as well as a control group without HI. In certain cases, a study design that only investigates the effect of

[11] National Institutes of Health, National Cancer Institute, *Protocol Template for Organ Dysfunction Studies*, as of August 15, 2023.

severe HI could be a reasonable approach to begin characterization of the effect of HI on the pharmacokinetics of a drug. In that case, if a significant effect is observed in subjects with severe HI, FDA recommends that the other HI subpopulations be studied. The sponsor should collect and report the etiology/etiologies of the underlying liver disease or other hepatic conditions that contributed to cirrhosis.

Laboratory parameters and clinical status should be stable prior to study enrollment. Sometimes, the repeat laboratory tests or ascites and encephalopathy scores can change substantially (e.g., > 30 percent change) prior to drug administration. In this case, laboratory test and ascites or encephalopathy assessment should be repeated (e.g., after one week) to allow the subject to be properly classified. If the severity of HI for a subject changed, the subject should be included in the severity group identified closest to pharmacokinetic sampling.

Sponsors should also consider that different etiologies of underlying liver diseases could affect a drug's pharmacokinetics or pharmacodynamics differently (e.g., cholestatic liver diseases may have a different impact on pharmacokinetics and/or pharmacodynamics compared to hepatocellular diseases that may be related to biliary excretion for drugs that undergo enterohepatic circulation).

For drugs under development for a liver disease, it could be important to enroll subjects with cirrhosis due to the target liver disease. Additionally, some drugs intended for the treatment of cancer should, due to safety considerations, only be administered to subjects with cancer who also have HI.

Study subjects should be excluded if they are experiencing acute liver disease (e.g., acute alcohol-associated hepatitis, acute viral hepatitis) or acute-on-chronic liver disease.

To the extent possible, subjects with normal hepatic function (i.e., the control group) and subjects with HI should have similar characteristics that are expected to affect the pharmacokinetics of the drug (e.g., age, sex, race or ethnicity, weight, phenotypes for polymorphic enzymes or transporters, if applicable). If subjects in the study use concomitant drugs, a careful assessment of their influence on pharmacokinetics or pharmacodynamics of the investigational drug should be made at the time of study planning.

For drugs whose pharmacokinetics is known to be affected by a polymorphic enzyme or transporter (e.g., CYP2D6, CYP2C9, CYP2C19; OATP1B1, BCRP, OCT1), the sponsor should determine the genotype of subjects during the screening phase.

2. Sample Size

The number of study subjects enrolled in each group should be sufficient to ensure precise estimation of the relevant pharmacokinetic parameters. Justification should be provided for the selected sample size. For example, one approach could be to prospectively target a 95 percent confidence interval within 60 to 140 percent of the point estimate of the geometric mean of the

relevant pharmacokinetic parameters for the drug in each HI group with at least 80 percent power.[12]

3. Drug Administration

A single-dose design is generally sufficient to describe the pharmacokinetics of the drug and its active metabolites when both exhibit dose-proportional and time-independent pharmacokinetics at anticipated therapeutic concentrations. A multiple-dose design, preferably at steady-state, should be considered when the drug or an active metabolite demonstrates non-dose-proportional or time-dependent pharmacokinetics.

Although the anticipated therapeutic dosage is generally recommended as the study dosage, a lower dosage may be appropriate in subjects with HI when dose-limiting toxicity is anticipated at higher drug concentrations. The rationale for the dosage selection should be included in the study protocol and study report.

If multiple routes of administration are proposed for a drug, the study should use the route of administration that is expected to result in the highest systemic exposure.

4. Sample Collection and Analysis

The concentrations of the parent drug and/or active metabolites should be evaluated in the appropriate matrix.

The sampling frequency and duration should be adequate to determine the relevant pharmacokinetic parameters of the parent drug and its active metabolites, in study subjects with HI.

For drugs that are highly extracted by the liver (extraction ratio >0.7) and are extensively bound to plasma proteins (fraction unbound <10 percent), the sponsor should determine the unbound fraction at trough and maximum plasma concentrations, as well as other concentration time points, when possible. The sponsor is encouraged to follow this recommendation for drugs with low hepatic extraction (extraction ratio <0.3) and extensive plasma protein binding to evaluate whether considerations based on total or unbound (free) drug concentrations are more appropriate. A rationale for not measuring unbound drug concentrations should be included in the study protocol and study report. Relevant pharmacokinetic parameters should be reported in terms of both unbound and total concentrations of drug, where applicable, in the study report.

For drugs not extensively bound to plasma proteins, the sponsor should retain and archive a sufficient quantity of the samples to allow for future drug binding studies to evaluate unexpected observations.

[12] Wang Y, PR Jadhav, M Lala, and J Gobburu, 2012, Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol, 52(10):1601-1606.

For drugs with stereochemical properties, stereoselectivity in drug metabolism and protein binding of enantiomers merits consideration.

C. Population Pharmacokinetic Approach

If subjects with varying degrees of HI are adequately represented in clinical trials (see section IV.A. Assessment of Hepatic Function), and there are sufficient drug concentration data to describe the pharmacokinetics of the drug, popPK analyses of data from clinical trials could be sufficient to characterize the impact of HI on drug exposure for the population represented in the trials. If subjects with HI cannot be enrolled in sufficient numbers, a dedicated HI pharmacokinetic study may be conducted to support appropriate dosage for the HI population not represented in clinical trials.

To allow for the successful use of a popPK approach or exposure-response analysis, the clinical trial design should retain some of the critical components of the dedicated HI studies described in sections IV.A and B of this guidance. FDA recommends the following:

- Including adequate numbers of subjects within each HI group
- Determining hepatic function using the appropriate classification system for the target population
- Maintaining accurate records of dosing and sample collection times
- Obtaining adequate numbers of samples per subject
- Measuring unbound drug concentrations when appropriate
- Measuring active metabolite levels, where applicable, in addition to levels of the parent drug
- Using the same method to classify hepatic function when data are pooled across studies
- Conducting exposure-response analyses, when available, accounting for HI as an independent predictor of response

For additional information on the application of popPK approaches, refer to the guidance for industry *Population Pharmacokinetics* (February 2022).

D. Considerations for Pharmacodynamic Assessments

Whenever appropriate, pharmacodynamic assessments should be included in HI studies. Such assessments are important in situations where HI could result in pharmacodynamic changes that are independent of pharmacokinetic changes (e.g., oral anticoagulants). In such situations, the pharmacokinetic and pharmacodynamic data could be critical to determine if a different dosage

in patients with HI is needed. The selection of the pharmacodynamic endpoints should be discussed with the relevant FDA review division.

Pharmacodynamic assessments can also be useful in studies designed to assess the impact of HI, especially if concentration-response data are not available, or if there are concerns that HI could alter the pharmacodynamic response. In situations where the relationship between pharmacokinetics and pharmacodynamics is unaltered, the pharmacokinetic measurements would be sufficient to characterize the impact of HI. However, when pharmacodynamics is studied, the pharmacodynamic endpoint can be chosen in one of two ways:

- The pharmacodynamic endpoint can be based on the pharmacological characteristics of the drug and/or its active metabolite(s).

- For drugs that are likely to affect integral components of hepatic function assessments, for example serum bilirubin or INR, one or more of these biomarkers can be studied.

V. DATA ANALYSIS

A. Estimating Parameters and Conveying Results

Plasma concentration data (and urine concentration data, if collected) should be analyzed to estimate measures or parameters describing the pharmacokinetics of the drug and/or its active metabolites, for example:

- Area under the plasma concentration-time curve (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 ($t_{1/2}$)
- Time to peak concentration (T_{max})
- Fraction unbound (f_u)

Pharmacokinetic parameters should be expressed in terms of unbound concentrations, where assessed, and total concentrations. Non-compartmental and/or compartmental modeling approaches to parameter estimates can be employed. The sponsor should provide the geometric and arithmetic means and measures of variability for pharmacokinetic parameters, the point estimate for the ratio of the means of the impaired and control groups for total and unbound AUC and C_{max}, and the associated 90 percent confidence interval.

B. Relationship Between Measures of Hepatic Function and Pharmacokinetics

Relationships should be explored between relevant pharmacokinetic parameters and individual components of the relevant hepatic classification systems using linear and nonlinear models. A

regression approach for continuous variables of the components of the relevant hepatic classification system as well as other relevant patient specific biomarkers and pharmacokinetic parameters should be considered to help identify relevant predictors of changes in pharmacokinetics and aid in refining dosage recommendations; however, some analyses may rely on categorical variables (e.g., CP Scores). The sponsor should calculate, and report estimates of the parameters of the chosen model as well as measures of their precision (e.g., standard errors or confidence intervals).

C. Development of Dosage Recommendations

Dosage recommendations in patients with HI should be based on the overall understanding of the relationship between hepatic function, drug exposure, and the exposure-response relationships for efficacy and safety. For drugs where small changes in exposure do not lead to clinically significant differences in the safety and effectiveness of the drug, the recommended dosage of the drug in patients with HI may be the same as in patients with normal hepatic function. When there is a need for a different recommended dosage in patients with HI compared to those with normal hepatic function, the dosage recommendations should be based on exposure-matching to a reference group with an acceptable benefit-risk profile, often the normal hepatic function group.

There are a number of approaches to dosage selection for patients with HI. For example, pharmacokinetic simulations that project systemic exposures that fall within the 5^{th} and 95^{th} percentiles of those achieved in the reference group can be used. Another approach is to establish no-effect boundaries, which represent an interval within which a change in systemic exposure is deemed not significant enough to warrant clinical action (see also section V.C.1 in the International Council for Harmonisation (ICH) guidance for industry *Drug Interaction Studies* (August 2024)).

VI. LABELING RECOMMENDATIONS

The Prescribing Information should include a summary of essential scientific information needed for the safe and effective use of the drug in patients with HI, as appropriate, and should include the following, as appropriate:

- Pharmacokinetics and pharmacodynamics in patients with HI
- Information on hepatic elimination of the drug and relevant active metabolites
- Clinical effects of the pharmacokinetic or pharmacodynamic changes in patients with HI
- Recommendations to prevent, mitigate, monitor for, or manage risks in patients with HI (e.g., different dosage or monitoring recommendations)

Guidance History[*]	Date	Description
Level 1 Draft Guidance	September 2026	See notice of availability for more information.**
Level 1 Final Guidance	May 2003	See notice of availability for more information.**

* This table was implemented beginning August 2026, and previous guidance history may not be captured in totality.

** The notice of availability is accessible via the Search for FDA Guidance Documents web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.