
Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing Guidance for Industry

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

**March 2024
Clinical Pharmacology**

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Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing Guidance for Industry¹

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I. INTRODUCTION

This guidance assists sponsors in the design and analysis of studies that assess the influence of impaired renal function on the pharmacokinetics (PK) and/or pharmacodynamics (PD) of an investigational drug, provides recommendations on how to determine the recommended dosage in patients with impaired renal function, and addresses how such information can inform the labeling, including:

- When a stand-alone study to assess a drug's PK in participants with impaired renal function is recommended and when it may not be warranted
- Design and conduct of pharmacokinetic studies in participants with impaired renal function
- Considerations for characterizing a drug's PK in patients receiving intermittent or continuous renal replacement therapies
- Using information from phase 2 and phase 3 studies to characterize the impact of renal function on PK and/or drug effects in patients with impaired renal function
- Considerations for deriving dosage recommendations for patients with impaired renal function
- Analysis and reporting of study results that characterize the impact of impaired renal function and how these data inform dosing recommendations in labeling

¹ This guidance has been prepared by the Renal Impairment Guidance Working Group in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

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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 guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

The kidneys are involved in the elimination of many drugs. The degree of renal excretion of an unchanged drug or its metabolites is the net result of glomerular filtration, tubular secretion, tubular reabsorption, and to a lesser degree, metabolism in the kidneys.² When a drug is eliminated primarily through renal excretion, patients with renal impairment frequently have different PK and may require a different recommended dosage than patients with normal kidney function.

Impaired renal function typically decreases renal excretion of the drug or its metabolites. However, impaired renal function has also been associated with changes in the absorption, plasma protein binding, or distribution of a drug. Impaired renal function can alter some drug metabolism and transport pathways in the liver and gut; thus, there is potential for renal impairment to also affect drugs that are predominantly cleared non-renally.^{3,4} These changes can be particularly prominent in patients with severely impaired renal function and those with kidney failure who have not yet been treated with renal replacement therapy. These topics are an area of active research, and the findings from this research could inform FDA guidance in the future.

As a result of the above considerations, it is important to characterize a drug's PK in patients with renal impairment to provide appropriate dosage recommendations. Exceptions where impaired renal function is not likely to alter PK to a clinically significant degree are described in section III.B. Circumstances Where a Dedicated Study May Not Be Warranted.

III. CONSIDERATIONS FOR RENAL IMPAIRMENT STUDIES

The recommended dosage of a drug for an indication is frequently the same dosage used in the key clinical studies that supported the safety and effectiveness of the drug for that indication. However, the eligibility criteria in key clinical studies sometimes exclude patients with impaired renal function. To address this issue, the FDA recommends that the effect of impaired renal function on a drug's PK be characterized early in drug development so that patients with

² Miners JO, X Yang, and L Zhang, 2017, The Role of the Kidney in Drug Eliminations: Transport, Metabolism, and the Impact of Kidney Disease on Drug Clearance, *Clin Pharmacol Ther*, 102:436-49.

³ Sun H, L Frassetto, and LZ Benet, 2006, Effects of Renal Failure on Drug Transport and Metabolism, *Pharmacol Ther*, 109:1-11.

⁴ Nolin TD, J Naud, FA Leblond, and V Pichette, 2008, Emerging Evidence of the Impact of Kidney Disease on Drug Metabolism and Transport, *Clin Pharmacol Ther*, 83:898-903.

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impaired renal function can be included (and appropriately dosed) in the late-phase clinical studies.

Early characterization can be based on data obtained from phase 1 or phase 2 studies. Alternatively, this information can be obtained by using modeling and simulation strategies, for example, physiologically based pharmacokinetic modeling and simulation. Such approaches allow sponsors to obtain clinical experience using the proposed dosing regimen in patients with impaired renal function and thus, better ensure that the study findings will be applicable to the population likely to use the drug, if approved.^{5,6}

Alternative enrollment designs, such as sequential or adaptive enrollment of patients with progressively worsening categories of renal function can also be considered to support the safe enrollment of patients.⁷ If a sponsor believes that such patients should be excluded from these studies, they should include a rationale for this exclusion in the protocol and discuss this exclusion with the FDA.

A. When a Dedicated Study Should be Conducted

1. Drugs Excreted Primarily by the Kidneys

A dedicated renal impairment study (described in section IV.B. Full Pharmacokinetic Study Design) is recommended when impaired renal function is likely to alter the PK of the drug or its active metabolites⁸ because they are substantially eliminated by the kidneys. A drug is considered to be substantially eliminated by the kidneys when the fraction of systemically available drug or active metabolite that is eliminated unchanged in the urine is 0.3 or greater.

2. Drugs Excreted Primarily by Other Routes

An impact of severe renal impairment on the PK of drugs predominantly eliminated via the hepatic route cannot always be excluded. In such situations, a reduced pharmacokinetic study design (described in section IV.C. Reduced Pharmacokinetic Study Design) should be considered.

⁵ See the FDA guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁶ See the FDA guidance for industry *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020).

⁷ Sahre MD, Milligan L, Madabushi R, Graham RA, Reynolds KS, Terzic A, Benjamin J, Burckart GJ, Huang SM, Schuck R, Thompson AM, Zineh I, 2021, Evaluating Patients With Impaired Renal Function During Drug Development: Highlights From the 2019 US FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting, *Clinical Pharmacology and Therapeutics*, 110(2): 285-8.

⁸ Active metabolites are moieties with known or suspected therapeutic or adverse activity.

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3. *Certain Therapeutic Proteins and Peptides*

Data from biologics license application reviews and the literature⁹ indicate that impaired renal function decreased the renal clearance of some therapeutic proteins and peptides with a molecular weight of less than 69 kDa. In some cases, the use of a lower dosage in patients with impaired renal function reduced the risk of exposure-related adverse reactions. Therefore, pharmacokinetic studies in participants with impaired renal function are recommended for therapeutic proteins and peptides with a molecular weight less than 69 kDa, unless the fraction of systemically available drug or active metabolite that is eliminated unchanged in the urine is less than 0.3. Assessing the effect of renal impairment on the PK of antibody-drug conjugates is also important.¹⁰

4. *Evaluating the Influence of Renal Replacement Therapies*

The PK of drugs that are likely to be used in patients receiving renal replacement therapies should be evaluated to determine the contribution of the specific replacement modality (e.g., intermittent or continuous) to the elimination of the drug and its potentially active metabolites (see section IV.E. Effect of Renal Replacement Therapies on the PK of a Drug). It can also provide information about the potential to use renal replacement therapies to remove the drug in overdose scenarios.

Dialysis- and filtration-based therapies can remove a significant fraction of a drug or its active metabolites, leading to clinically significant exposure changes. In such cases, a change in the dosing regimen could be appropriate.

Intermittent hemodialysis (IHD) is currently the most common dialysis modality used in patients being treated with renal replacement therapy in the United States. Therefore, to evaluate the impact of dialysis on the PK of a drug, we recommend that sponsors conduct these studies in patients undergoing IHD. Similar principles can be applied to characterize the impact of peritoneal dialysis or continuous renal replacement therapy (CRRT) on the disposition of the drug and/or its active metabolites.

A study of the effect of renal replacement therapies on the PK of a drug may not need to be conducted if the procedure is unlikely to result in significant elimination of the drug or its active metabolites, for example, if the drug:

- Has a molecular weight that makes it unlikely to be cleared by the renal replacement modality

⁹ Meibohm B and H Zhou, 2012, Characterizing the Impact of Renal Impairment on the Clinical Pharmacology of Biologics, *J Clin Pharm*, 52:54S-62S.

¹⁰ For more information, see the FDA guidance for industry *Clinical Pharmacology Considerations for Antibody-Drug Conjugates* (March 2024).

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- Exhibits high plasma protein binding that is not affected by renal impairment, making it unlikely to be cleared by the renal replacement modality

B. Circumstances Where a Dedicated Study May Not Be Warranted

For some drugs, impaired renal function is not likely to alter the PK of a drug enough to justify a different dosage compared to patients with normal renal function. The following are examples where the PK are not expected to be markedly different between patients with normal or impaired renal function. In such cases, a dedicated study may not be warranted.

- Gaseous or volatile drugs and active metabolites that are primarily eliminated through the lungs
- Drugs intended only for single administration
- Therapeutic proteins with a molecular weight greater than 69 kDa
- Locally acting drugs with limited or no systemic exposure

IV. STUDY DESIGN

The primary goal of the renal impairment study is to characterize the impact of impaired renal function on the PK of the drug and determine whether the extent of the changes in the PK of the drug warrants a different recommended dosage in patients with impaired renal function. Achieving this goal can be accomplished in a variety of ways, depending on the characteristics of the drug and the intended patient population. This section discusses:

- Determination of renal function in adults
- Design of a full pharmacokinetic study
- Design of a reduced pharmacokinetic study
- Evaluation of the impact of impaired renal function on the PK of a drug in phase 2 or phase 3 studies
- Design of studies in patients receiving renal replacement therapies
- Considerations for pharmacodynamic or other response assessments

A. Determination of Renal Function

There are different ways to assess renal function. Measurement of the glomerular filtration rate (GFR) using exogenous markers (e.g., inulin, iothalamate, iohexol) provides a more accurate assessment of renal function than estimating equations. In addition, measured creatinine

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clearance (CL_{cr}) using timed urine samples is sometimes used to assess renal function. However, these methods are not routinely used in clinical practice. For pharmacokinetic studies, estimation of renal function using a contemporary and widely accepted equation, is usually sufficient.

Equations for estimation of renal function in adults include the following:

- (1) **Estimated GFR (eGFR) calculated using a contemporary, widely accepted equation for the population being studied:**^{11,12} In clinical practice, eGFR is commonly referenced to a body surface area (BSA) value of 1.73 m² and expressed in units of mL/minute/1.73 m². However, renal clearance of a drug is proportional to the individual's GFR (expressed as mL/minute). Hence, when providing a recommended dosage in adult patients with renal impairment, use the eGFR expressed as mL/minute rather than the eGFR referenced to a BSA value of 1.73 m².¹³ To compute eGFR in mL/minute, multiply the eGFR referenced to a BSA of 1.73 m² with the individual's BSA (calculated using an appropriate formula)^{14,15} and divide by 1.73.
- (2) **Estimated CL_{cr} (eCL_{cr}) in mL/minute calculated using the Cockcroft-Gault (C-G) equation:**¹⁶ In overweight or obese individuals, use of alternative body weight metrics such as ideal body weight (IBW) or adjusted body weight (ABW) when calculating eCL_{cr} using the C-G equation is likely to provide a more accurate estimate of renal function than using actual body weight.¹⁷

¹¹ Levey AS, LA Stevens, CH Schmid, YL Zhang, AF Castro 3rd, HI Feldman, JW Kusek, P Eggers, F Van Lente, T Greene, J Coresh, and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), 2009, A New Equation to Estimate Glomerular Filtration Rate, *Ann Intern Med*, 150(9):604-12.

¹² Titan S, S Miao, H Tighiouart, N Chen, H Shi, L Zhang, Z Li, M Froissart, P Rossing, A Grubb, L Fan, M Mauer, O Bakoush, C Wyatt, MG Shlipak, T Shafi, LA Inker, and AS Levey, 2020, Performance of Indexed and Nonindexed Estimated GFR, *Am J Kidney Dis*, 76(3):446-9.

¹³ See Section IV.E. of the draft guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023). When final this guidance, will represent the FDA's current thinking on this topic.

¹⁴ Dubois D and EF Dubois, 1916, A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, *Arch Intern Med*, 17:863-871.

¹⁵ Mosteller RD, 1987, Simplified Calculation of Body Surface Area, *N Engl J Med*, 317:1098.

¹⁶ Cockcroft DW and MH Gault, 1976, Prediction of Creatinine Clearance from Serum Creatinine, *Nephron*, 16(1):31-41.

¹⁷ Pai MP, 2010, Estimating the Glomerular Filtration Rate in Obese Adult Patients for Drug Dosing, *Advances in Chronic Kidney Disease*, 17(5):e53-e62.

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Because of the widespread availability and incorporation of eGFR into current clinical practice, use of eGFR to determine renal function in PK studies is recommended over eCLcr.^{18,19} However, given the strengths and limitations of each method, use of measured GFR (using an exogenous marker), measured CLcr, or any contemporary, widely accepted, and clinically applicable estimating equation for the population being studied is considered reasonable to assess renal function in pharmacokinetic studies.

In pediatric patients, renal function can also be either measured or estimated. There are multiple equations for estimation, and, as with adults, any widely accepted contemporary equation for use in the appropriate pediatric age range is acceptable.²⁰

B. Full Pharmacokinetic Study Design

A full pharmacokinetic study design is recommended for drugs that are described in section III.A.1 Drugs Excreted Primarily by the Kidneys. The recommended characteristics for the full pharmacokinetic study design are provided in the sections below.

1. Study Participants

To adequately characterize the impact of impaired renal function on the PK of a drug, the renal function of study participants should range from normal function to severe impairment or kidney failure not on dialysis. The classification of renal function described in Table 1 can be used to enroll participants into the dedicated renal impairment study.

¹⁸ Hudson JQ and TD Nolin, 2018, Pragmatic Use of Kidney Function Estimates for Drug Dosing: The Tide is Turning, *Advances in Chronic Kidney Disease*, 25(1):14-20.

¹⁹ Matzke GR, GR Aronoff, AJ Atkinson Jr, WM Bennett, BS Decker, KU Eckardt, T Golper, DW Grabe, B Kasiske, F Keller, JT Kielstein, R Mehta, BA Mueller, DA Pasko, F Schaefer, DA Sica, LA Inker, JG Umans, and P Murray, 2011, Drug Dosing Consideration in Patients With Acute and Chronic Kidney Disease: A Clinical Update From Kidney Disease: Improving Global Outcomes (KDIGO), *Kidney International*, 80(11):1122-1127.

²⁰ For recommendations on assessing renal function in pediatric patients, refer to the FDA draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (September 2022). When final this guidance, will represent the FDA's current thinking on this topic.

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Table 1. Classifications of Renal Function^{a,b} for Dedicated Renal Impairment Studies^{c, d}

Description	Range of Values for Renal Function (mL/minute)
Control (normal renal function)	≥ 90
Mild impairment	$60 < 90$
Moderate impairment	$30 < 60$
Severe impairment and kidney failure not receiving dialysis	< 30

^a eGFR: estimate of GFR based on an estimation equation and expressed in mL/minute. To convert mL/minute/1.73 m² to mL/minute multiply by the individual's BSA calculated using an appropriate formula and divide by 1.73.

^b eCLcr: estimated creatinine clearance based on the C-G equation.

^c This classification is strictly for the purposes of conducting a dedicated renal impairment study and is not intended to be used for the purposes of classifying kidney disease.

^d Study participants should be enrolled based on one common estimation method to determine renal function in control and renal impairment groups.

Participants with impaired renal function should have stable renal function (i.e., patients with acute changes in renal function should not be included in the studies discussed in this section).

In general, participants with impaired renal function should be similar to the control group with respect to factors known to affect the drug's PK, for example, demographics (e.g., age, sex, race, ethnicity), pharmacogenetic factors, or weight. Participants taking drugs that are likely to impact drug metabolism or excretion should be excluded from renal impairment studies.

2. Sample Size

The number of participants enrolled in each renal function group should be sufficient to ensure a precise estimation of the relevant pharmacokinetic parameters. Justification should be provided for the sample size selected. For example, one approach could be to prospectively target a 95 percent confidence interval within 60 percent and 140 percent of the geometric mean estimate of relevant pharmacokinetic parameters for the drug in each renal function group with at least 80 percent power.²¹

3. Drug Administration

²¹ 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.

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A single-dose study is usually sufficient to accurately describe the PK of the drug and its active metabolites, especially when the drug and active metabolites exhibit dose-proportional and time-independent PK at the concentrations anticipated in the patients to be studied. In rare cases, for example, when the drug shows time-dependent PK, a multiple-dose study, preferably dosed to steady-state, should be considered.

In most single-dose studies, the same dose can be administered to all participants regardless of renal function, because the peak concentration of a drug is usually not substantially increased by renal impairment. In multiple-dose studies, lower doses or less frequent administration can be considered in patients with impaired renal function to prevent the accumulation of the drug and its metabolites. The dosage can be adjusted based on the best available pre-study prediction of the PK of the drug and its active metabolites in patients with impaired renal function. In multiple-dose studies, the dosing should be continued long enough to achieve steady-state. A loading dose strategy can be considered to shorten the time to reach steady-state, particularly if the elimination half-life is greatly prolonged in patients with impaired renal function.

4. Sample Collection and Analysis

Plasma or whole blood should be collected and analyzed for the parent drug and any active metabolites. Collection of urine samples should be considered when the drug is primarily renally cleared. The frequency and duration of plasma sampling and urine collection should be sufficient to accurately estimate the relevant pharmacokinetic parameters for the parent drug and its active metabolites (see section V. Data Analysis).

Plasma protein binding is often altered in patients with impaired renal function. For systemically circulating active drugs and metabolites, the unbound concentrations generally determine the rate and extent of delivery to the sites of action. Measurement of unbound drug concentrations is recommended for each plasma sample only if the binding is concentration-dependent or is affected by metabolites or other time-varying factors. Otherwise, the unbound fraction should be determined using a limited number of samples or even a single sample from each patient. For drugs and metabolites with a low extent of plasma protein binding (e.g., less than 90 percent), changes in PK resulting from alterations in protein binding due to impaired renal function are generally expected to be small relative to those in patients with normal renal function. In such cases, a description and analysis of the PK of the drug or metabolite in terms of total concentrations is sufficient.

C. Reduced Pharmacokinetic Study Design

For drugs that are predominantly eliminated via nonrenal routes and likely to be used in patients with impaired renal function, a reduced pharmacokinetic study design can be used to determine the need for a different dosage than for patients with normal renal function. The intent of a reduced pharmacokinetic study design is to represent a *worst-case* scenario, i.e., one that shows the greatest impact that impaired renal function could have on the PK of the drug. Prior submissions to the Agency and literature reports suggest that for such a study, participants with

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severe renal impairment or kidney failure not on dialysis (see Table 1) can be considered to represent the worst-case scenario.²²

If a reduced pharmacokinetic study shows a clinically relevant effect on the PK of the drug in participants with severe renal impairment or kidney failure not on dialysis, the sponsor should characterize the effect of impaired renal function on the drug's PK in participants with the other levels of impaired renal function (see Table 1). If no difference in PK is observed between participants with severe renal impairment or kidney failure not on dialysis compared to normal renal function, then no further study is recommended. Other study design considerations described in sections IV.B. Full Pharmacokinetic Study Design also apply to the reduced design.

D. Characterizing the Impact of Renal Function in Phase 2 and Phase 3 Studies

If there is adequate representation of patients with varying degrees of renal function in clinical studies (see section III. Considerations For Renal Impairment Studies), as well as sufficient data to describe the impact of impaired renal function on the PK of the drug, population pharmacokinetic (popPK) analyses of data from phase 2 and/or phase 3 clinical studies could be sufficient to characterize the impact of renal function on drug exposure for the population that was represented in the studies. If patients with severe renal impairment were not enrolled in sufficient numbers, a reduced pharmacokinetic design study may be needed to provide appropriate dosing recommendations in labeling for the impaired renal function population not represented in clinical studies. When possible, renal function should be assessed as an independent predictor of exposure-response relationships.

To allow for the successful use of a popPK approach or exposure-response analysis, the study design should retain some of the critical components of the dedicated renal impairment studies described in the previous section on full study designs (section IV.B. Full Pharmacokinetic Study Design). The following are important considerations:

- Sufficient numbers of participants over a wide range of renal function
- Accurate records of dosing and sample collection times
- Adequate numbers of samples per participant
- Unbound drug concentrations when appropriate
- Active metabolite levels, where applicable, in addition to levels of the parent drug

²² Zhang L, N Xu, S Xiao, V Arya, P Zhao, LJ Lesko, and SM Huang, 2012, Regulatory Perspectives on Designing Pharmacokinetic Studies and Optimizing Labeling Recommendations for Patients with Chronic Kidney Disease, *J Clin Pharmacol*, 52(1 Suppl):70S-90S.

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- Use of the same equation to estimate renal function, especially when data are pooled across studies
- Exposure-response analyses, when available, should account for impaired renal function as an independent predictor of response

For additional information on the application of popPK or exposure-response analysis approaches, refer to the FDA guidances for industry *Population Pharmacokinetics* (February 2022) and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003), respectively.

E. Effect of Renal Replacement Therapies on the PK of a Drug

The primary questions to be addressed by studying the effect of renal replacement therapies on the PK of a drug are: (1) whether there will be a different recommended dosage, and if so, what will be the dosage; and (2) the timing of drug administration relative to renal replacement therapy. The results of the study may also provide insight regarding the value of renal replacement therapy for the treatment of a drug overdose.

1. Intermittent Renal Replacement Therapies

This section mainly focuses on IHD, as it is currently the most common renal replacement therapy used in the United States. However, some of the general study design principles described below for IHD can be applied to other intermittent modalities.

It is critical for the IHD study to include both on- and off-dialysis periods. Each participant should receive a single dose on two occasions, once with the dose administered prior to a dialysis session, with dialysis typically commencing just before the anticipated time to maximum concentration (T_{max}) following administration of the drug. On the second occasion, the drug should be administered in such a way that it reflects the exposures expected during an off-dialysis day (e.g., if the patient is dialyzed Monday/Wednesday/Friday, the off-dialysis day could be Tuesday).

Because most dialysis centers in the United States currently use high-flux dialyzers during IHD, pharmacokinetic studies should be conducted in patients being treated with high-flux IHD. It is important to record the blood flow (Q_B), dialysate flow (Q_D), ultrafiltration clearance (Q_{UF}), and the make and model of the dialyzer used in the study to interpret study results and extrapolate to other dialysis conditions.

2. Continuous Renal Replacement Therapies

For drugs likely to be used in critically ill patients on CRRT, the findings from IHD studies might not be sufficient to derive dosage recommendations for patients receiving this dialysis modality. Therefore, it is important to evaluate the impact of CRRT on the PK of the drug to derive appropriate dosage recommendations. Given the practical challenges (e.g., the hemodynamic instability of patients and the difficulty in obtaining blood samples) associated

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with conducting such a study, planning optimal sampling times is critical for the collection of relevant pharmacokinetic information in this setting. In addition, the methods for CRRT vary widely across institutions. To the extent possible, it is important to design and conduct these studies so that the results are generalizable across CRRT settings. A single-dose study is acceptable and may be the most feasible approach. Multiple-dose assessments can characterize the effect of CRRT as a patient's condition changes and should be considered when feasible. One approach that could allow collection of information that informs dosage is to use a fixed blood flow rate (Q_B) with multiple commonly prescribed effluent flow rates (Q_E) for each CRRT modality.²³ Sponsors are strongly encouraged to seek FDA's input early in the process of designing such studies.

3. *Sample Collection and Data Analysis*

a. IHD

To accurately estimate the clearance in patients undergoing IHD during the non-dialysis (or between dialysis) period, administration times and sampling times should be planned to capture the full pharmacokinetic profile of the drug and, where applicable, its active metabolites.

To determine the clearance during dialysis, blood samples should be collected pre-dialysis and at appropriate intervals during the dialysis period. The entire dialysate should be collected, its volume recorded, and a sample retained to determine drug concentrations.

Concentrations of the drug and any active metabolites should be measured in the blood entering the dialyzer as well as dialysate samples. The total amount of drug removed in the dialysate should be determined. The dialysis clearance (CL_D) can be calculated from the equation below, where t_0 marks the start time, and t_1 is the time of termination of the hemodialysis session:

$$CL_D = \frac{\text{Amount Recovered}}{AUC_{t_0-t_1}}$$

In certain cases (e.g., instability of the analyte in the dialysate), it could be possible to use the *A-V difference method*²⁴ to derive the dialysis clearance. With this approach, sampling of blood entering and leaving the dialyzer (the arterial and venous side) over the dialysis period is necessary. In addition, hematocrit and blood-to-plasma partitioning should be considered, among potential other potential factors. When using this method, it could still be useful to collect the dialysate for measurement for some time (e.g., 2 hours), to obtain verification of the values obtained with the A-V difference method.

²³ Nolin TD, GR Aronoff, WH Fissell, L Jain, R Madabushi, K Reynolds, L Zhang, SM Huang, R Mehrotra, MF Flessner, JK Leyboldt, JW Witcher, I Zineh, P Archdeacon, P Roy-Chaudhury, and SL Goldstein, 2015, Pharmacokinetic Assessment in Patients Receiving Continuous RRT: Perspectives from the Kidney Health Initiative, Clin J Am Soc Nephrol, 10(1):159–164.

²⁴ Atkinson AJ, Nolin TD, Allen JM, 2022, Pharmacokinetics in Patients Requiring Renal Replacement Therapy, from Atkinson's Principles of Clinical Pharmacology (Fourth Edition), Chapter 6, pages 73-90, Academic Press.

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Blood samples before and at the end of dialysis should also be used to measure drug binding to plasma proteins. The fraction of the administered dose that is recovered in the dialysate should be calculated to assess the need for administering supplemental drug doses to hemodialysis patients.

The analysis should also consider the potential for a rebound due to redistribution of drug or active metabolites from peripheral tissues after dialysis and characterize its implications for dosage recommendations.

b. CRRT

In addition to collecting simultaneous pre-filter, post-filter, and effluent samples for drug and active metabolites, additional time-matching data measuring CRRT therapy intensity (e.g., blood flow rate, replacement fluid flow rate, ultrafiltration rate, dialysis flow rate) should be captured to determine extracorporeal clearance (CL_{EC}). Samples taken prior to CRRT initiation, when therapy is halted, or during a change in the filter could also be used to estimate drug clearance associated with other elimination pathways (e.g., non-renal elimination).

F. Considerations for Pharmacodynamic Assessments

Whenever appropriate and feasible, pharmacodynamic assessments should be included in renal impairment studies. Such assessments are important in situations where impaired renal function can 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 the appropriate recommended dosage in patients with impaired renal function. The selection of the pharmacodynamic endpoints should be discussed with the relevant review division.

V. DATA ANALYSIS

A. Estimating Pharmacokinetic Parameters

Plasma concentration data and, where available, urinary excretion data should be analyzed to estimate pharmacokinetic parameters of the drug and its active metabolites. The pharmacokinetic parameters of interest include the area under the plasma concentration-time curve (AUC), peak concentration (C_{max}), fraction unbound (f_u), apparent clearance (CL/F), renal clearance (CL_R), apparent nonrenal clearance (CL_{NR}/F), apparent volume of distribution (V/F), and effective and terminal half-life ($t_{1/2}$), where applicable. The pharmacokinetic parameters of active metabolites can include the AUC, C_{max} , CL_R , and $t_{1/2}$. Non-compartmental and/or other model-based approaches to parameter estimation can be employed. For renal replacement therapy, the dialytic clearance (CL_D) (for intermittent hemodialysis) or the extracorporeal clearance (CL_{EC}) (for CRRT) should be estimated (see section IV.E Effect of Renal Replacement Therapies on the PK of a Drug).

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B. Modeling the Relationship Between Renal Function and Pharmacokinetic Parameters

The FDA recommends a regression approach in which estimated individualized renal function and the pharmacokinetic parameters are treated as continuous variables. This method is usually preferred to an analysis in which estimated renal function is treated as a categorical variable corresponding to the normal, mild, moderate, and severe renal impairment as well as kidney failure not on dialysis groups (see Table 1), because it allows the identification of thresholds that could be more meaningful for derivation of dosage adjustments. In either case, the potential for confounding due to differences in baseline covariates that can affect a drug's PK (e.g., age, sex, race, ethnicity, weight) should be evaluated.

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. Developing Dosage Recommendations in Patients with Impaired Renal Function

Dosage recommendations in patients with impaired renal function should be determined based on the overall understanding of the relationship between renal function, drug exposure, and the exposure-response relationships (efficacy and safety). For drugs with a wide therapeutic range, changes in the drug's PK based on renal function might not always result in a different recommended dosage in patients with impaired renal function. When there is a need for a different dosage recommendation for patients with impaired renal function, these dosage recommendations should be based on exposure-matching to a reference group with an acceptable benefit-risk profile for the drug. Hence, the reference group does not have to be limited to the normal renal function group.

There are several approaches to dosage selection for patients with impaired renal function. For example, pharmacokinetic simulations that project systemic exposures that fall within the 5th and 95th 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.B.1 in the FDA guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)).

The sponsor should use the data from modeling and simulation to determine the level of renal function for which a different dosage is recommended. It is not always necessary to rely on pre-specified categories of impaired renal function as shown in Table 1.

In some situations, dosage recommendations in patients with impaired renal function can significantly differ if different estimating equations of renal function are used. Hence, as a good practice, it is important to evaluate the impact of different contemporary estimating equations of renal function on drug dosing recommendations. In such situations, it is important to understand the reasons underlying the discrepant results.

Contains Nonbinding Recommendations

There are some considerations specific to renal replacement dosing. Dosage recommendations in patients receiving renal replacement therapy should be determined based on the overall understanding of the relationship between extracorporeal clearance (CL_{EC}), drug exposure, and exposure-response relationships. CL_{EC} should be calculated based on the specific modality being evaluated. In CRRT, dosing recommendations should be based on the intensity of the CRRT regimen, as CL_{EC} is known to be influenced by the prescribed blood, dialysis, and ultrafiltration flow rates. Dose and/or dosing interval adjustments can be recommended to correct for clinically relevant changes in drug exposure. There may be different recommended dosages for different filter types and CRRT modalities. The sponsor should provide data/justification to inform the dosage recommendations for other CRRT modalities. A different recommended dosage should also be considered in situations when CRRT therapy is interrupted for a significant period of time, or patients experience changes in residual renal function during the course of CRRT therapy.

VI. LABELING RECOMMENDATIONS

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

- PK and PD in patients with impaired renal function, including those receiving dialysis
- Information on renal elimination of the drug and relevant active metabolites
- Clinical effects of pharmacokinetic or pharmacodynamic changes in patients with impaired renal function
- Recommendations to prevent, mitigate, monitor for, or manage risks in patients with impaired renal function (e.g., different dosage or monitoring recommendations)