Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

For questions regarding this draft document contact the CDER, Office of Clinical Pharmacology's 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 2020
Clinical Pharmacology
Revision 2

Guidance for Industry

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

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

September 2020
Clinical Pharmacology

Revision 2

TABLE OF CONTENTS

Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance assists sponsors in the design and analysis of studies[2] that assess the influence of impaired renal function on the pharmacokinetics (PK) and/or pharmacodynamics (PD) of an investigational drug and addresses how such information can inform the labeling. This version[3] revises and replaces the draft guidance entitled *Pharmacokinetics in Patients With Impaired Renal Function — Study Design, Data Analysis and Impact on Dosing and Labeling* (March 2010) and provides updated recommendations on the following topics:

- When a standalone study of a drug's PK in subjects with impaired renal function is recommended and when it may not be needed
- The design and conduct of pharmacokinetic studies in subjects with impaired renal function
- Considerations for characterizing a drug's PK in patients undergoing intermittent or continuous dialytic therapies

[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).

[2] For the purposes of this guidance, studies and trials are used interchangeably.

[3] The updates in this guidance are in part based on the discussion at an FDA Advisory Committee Meeting in May 2019: https://www.fda.gov/advisory-committees/advisory-committee-calendar/may-7-2019-meeting-pharmaceutical-science-and-clinical-pharmacology-advisory-committee-meeting#event-materials.

- The use of pharmacokinetic information from phase 2 and 3 studies to inform dosing recommendations for patients with impaired renal function

- The analysis and reporting of the results of studies that characterize the impact of impaired renal function and how these data inform dosing recommendations in labeling

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 are to 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

Drugs are eliminated from the body by a variety of mechanisms. Most drugs are cleared by a combination of some or all of the following pathways: metabolism and transport in the small intestine, metabolism and transport in the liver, and glomerular filtration and tubular secretion of unchanged drug by the kidneys (i.e., renal excretion). If a drug is eliminated primarily through renal excretion, then impaired renal function usually alters the drug's PK to an extent that a change in the dosage regimen from that used in patients with normal renal function should be considered.

The most obvious type of change in the PK of a drug arising from impaired renal function is a decrease in renal excretion of the drug or its metabolites. However, impaired renal function has also been associated with changes in the absorption, plasma protein binding, and/or tissue distribution of a drug. Literature reports indicate that impaired renal function can alter some drug metabolism and transport pathways in the liver and gut.[4,5] These changes can be particularly prominent in patients with severely impaired renal function. 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, for most drugs that are likely to be administered to patients with impaired renal function, it is important to characterize a drug's PK in subjects with impaired renal function to provide appropriate dosing recommendations. Exceptions to this recommendation are described in section I.C.

[4] Sun, H, L Frassetto, and LZ Benet, 2006, Effects of Renal Failure on Drug Transport and Metabolism, Pharmacol Ther, 109:1–11.

[5] 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.

III. CONSIDERATIONS FOR RENAL IMPAIRMENT STUDIES

The safety and effectiveness of a drug are generally established for specific dosage regimens in late-phase clinical trials that enroll patients from the target patient population. Frequently, individuals with advanced renal disease are explicitly excluded from participation in these trials. Drug development programs should include an early characterization of the expected effect of impaired renal function on a drug's PK, with the goal of enabling the inclusion of this population in late-phase trials by allowing appropriate prospective dosage adjustment.

Early characterization can be based on data obtained from phase 1 and/or phase 2 studies. Alternatively, this information can be obtained by utilizing 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 trial findings will be applicable to the population likely to use the drug, should it be approved.[6, 7]

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. The exclusion of patients with impaired renal function from clinical studies conducted for a development program should be justified and discussed with the relevant review divisions.

A. Circumstances Where a Dedicated Study Is Recommended

1. Drugs Excreted Primarily Via Renal Mechanisms

A dedicated renal impairment study is generally recommended: (1) when the drug is likely to be used in such patients; and (2) when impaired renal function is likely to alter the PK of the drug or its active metabolites because they are substantially eliminated by the renal route. A drug is considered to be substantially eliminated by the renal route when the fraction of systemically available drug or active metabolite that is eliminated unchanged in the urine (f_e) is 0.3 or greater.

[6] See the FDA draft guidance entitled *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic. 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.

[7] See the FDA final guidance entitled *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry* (July 2020).

2. Certain Biologic Drugs (Therapeutic Proteins and Peptides)

Data from biologics license application reviews indicate that impaired renal function decreased the renal clearance of therapeutic proteins and peptides that have a molecular weight of less than 69 kDa. In some cases, a dose adjustment was necessary to reduce the risk of exposure-related toxicity in patients with impaired renal function. Therefore, pharmacokinetic studies in patients with impaired renal function are recommended for therapeutic proteins and peptides with a molecular weight less than 69 kDa.

3. Evaluating the Influence of Dialytic Therapies

The PK of drugs that are likely to be used in patients with end-stage renal disease (ESRD) undergoing dialysis should be evaluated both while the patient is on dialysis and off dialysis to determine the contribution of the dialytic method to the elimination of the drug and its potentially active metabolites (see section I.E). Dialytic 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 dosage regimen, such as a supplemental dose following the dialysis procedure, could be appropriate.

Intermittent hemodialysis (IHD) is the most common dialytic modality used in patients with ESRD 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. When relevant to the intended patient population, 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 metabolites.

A study of the effect of dialytic therapies on the PK of a drug can be omitted if the dialytic 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 dialytic modalities
- Exhibits high plasma protein binding that is not affected by impaired renal function

B. Circumstances Where a Dedicated Study Can Be Considered

As mentioned in section II, it is often important to characterize the impact of impaired renal function on the PK of drugs that are eliminated predominantly via nonrenal routes. In such situations, a reduced pharmacokinetic study design (described in section I.C) can be considered.

C. Circumstances Where a Dedicated Study May Not Be Important

For some drugs, impaired renal function is not likely to alter the PK of a drug enough to justify dosage adjustment. In such cases, a dedicated study is generally not necessary. Current knowledge suggests that the following drug properties justify this approach:

- Gaseous or volatile drugs and active metabolites that are primarily eliminated through the lungs
- Drugs intended only for single-dose administration
- Therapeutic proteins with a molecular weight greater than 69 kDa
- Locally acting drugs (e.g., topical products) with limited systemic absorption

IV. STUDY DESIGN

The primary goal 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 warrant a dose adjustment. 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 dialytic 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 such as inulin, iothalamate, EDTA, diethylene triamine pentaacetic acid, and iohexol provides a more accurate assessment of renal function than estimating equations. In addition, measured creatinine clearance (CLcr) using timed urine samples is sometimes used to assess renal function. However, these methods are not routinely

used in clinical practice and estimation of renal function using a widely accepted serum creatinine-based equation is usually sufficient for pharmacokinetic studies.

Serum creatinine-based equations include:

(1) Estimated GFR (eGFR) calculated using a contemporary, widely accepted equation for the population being studied.[8,9] In clinical practice, eGFR values are standardized to a body surface area (BSA) value of 1.73 m^2 and expressed and reported in units of mL/min/1.73 m^2. Renal clearance of a drug is proportional to individual GFR (expressed as mL/min) and not BSA-standardized GFR, hence BSA-standardization will not be appropriate in patients with BSAs different than the standard (1.73 m^2). To individualize GFR for drug dosing, multiply the standardized GFR by the individual's BSA calculated using an appropriate formula[10,11] and divide by 1.73.

(2) Estimated creatinine clearance (CLcr) in mL/min calculated using the Cockcroft-Gault (C-G) equation.[12] In overweight or obese individuals, use of alternative body weight metrics such as ideal body weight (IBW) or adjusted body weight (ABW) when calculating CLcr is likely to provide a more accurate estimate of renal function than total body weight.[13]

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

[9] Levey AS, J Coresh, T Greene, LA Stevens, YL Zhang, S Hendriksen, JW Kusek, F Van Lente, Chronic Kidney Disease Epidemiology Collaboration, 2006, Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate, Ann Intern Med, 145(4):247-54.

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

[11] Mosteller RD, 1987, Simplified Calculation of Body Surface Area, N Engl J Med, 317:1098.

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

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

Because of the widespread availability and incorporation of eGFR into current clinical practice, use of eGFR to determine renal function in pharmacokinetic studies is recommended.[14, 15] 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 PK 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 pediatric patients is acceptable. In pediatric patients below two years of age, maturation, gestational age and other factors need to be taken into account. Therefore, early communication with the Agency is recommended. For our draft recommendations on assessing renal function in pediatric patients, refer to the FDA draft guidance for industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014).[16]

B. Full Pharmacokinetic Study Design

A full PK study design is recommended for drugs that are described in Section III.A.

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. The classification of renal function described in Table 1 can be used to enroll participants into the dedicated renal impairment study. It can also help derive dosing recommendations.

[14] 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.

[15] 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, 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.

[16] When final, this guidance will represent the FDA's current thinking on this topic.

Table 1. Classifications of Renal Function[a,b] for Dedicated Renal Impairment Studies

Description	Range of Values for Renal Function (mL/min)
Control (normal renal function)	≥ 90
Mild impairment	60-89
Moderate impairment	30-59
Severe impairment	15-29
Kidney failure[c]	<15 or dialysis patients on non-dialysis days

[a] eGFR: estimate of GFR based on an estimation equation and expressed in mL/min. To convert mL/min/1.73 m^2 to mL/min multiply by the individual's BSA calculated using an appropriate formula and divide by 1.73.

[b] CLcr: estimated creatinine clearance based on the C-G equation.

[c] Kidney failure: This classification is strictly for the purposes of conducting a dedicated renal impairment study and should not be used for the purposes of classifying kidney disease.

To characterize the impact of impaired renal function on the PK of drugs that are expected to have a wide therapeutic range, study subjects can be stratified based on renal function ≥60 mL/min (normal renal function or mild renal impairment), 15-59 mL/min (moderate to severe renal impairment), and <15 mL/min or dialysis patients on non-dialysis days.

Subjects with impaired renal function should be hemodynamically stable. Further, subjects with impaired renal function should be similar to the reference group with respect to factors known to affect the drug's PK. Subjects taking medications that are likely to impact drug metabolism or excretion should be excluded from renal impairment studies.

Ideally, the control group in this study should be representative of the typical patient population for the drug under study, considering the patients' renal function and other factors known to affect the drug's PK.

2. Sample Size

The number of subjects enrolled in each renal function group should be sufficient to ensure 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

267 percent power.[17]
268
269 *3. Drug Administration*
270
271 A single-dose study is usually sufficient to accurately describe the PK of the drug and its active
272 metabolites, especially when the drug and active metabolites exhibit dose-proportional and time-
273 independent PK at the concentrations anticipated in the patients to be studied. In rare cases, e.g.
274 when the drug shows dose- or time-dependent PK, a multiple-dose study should be conducted.
275
276 In most single-dose studies, the same dose can be administered to all patients regardless of renal
277 function, because the peak concentration of a drug is not substantially affected by renal function.
278 In multiple-dose studies, lower doses or less frequent administration can be considered in
279 patients with impaired renal function to prevent the accumulation of the drug and its metabolites.
280 The dosage regimen can be adjusted based on the best available pre-study estimates of the PK of
281 the drug and its active metabolites in patients with impaired renal function. In multiple-dose
282 studies, the dosing should be continued long enough to achieve steady-state drug levels. A
283 loading dose strategy can be considered to shorten the time to reach steady-state drug levels,
284 particularly if the elimination half-life is greatly prolonged in patients with impaired renal
285 function.
286
287 *4. Sample Collection and Analysis*
288
289 Plasma or whole blood as well as urine samples should be collected and analyzed for the parent
290 drug and any metabolites of interest. The frequency and duration of plasma sampling and urine
291 collection should be sufficient to accurately estimate the relevant pharmacokinetic parameters for
292 the parent drug and its active metabolites (see section V).
293
294 Plasma protein binding is often altered in patients with impaired renal function. For systemically
295 active drugs and metabolites, the unbound concentrations generally determine the rate and extent
296 of delivery to the sites of action. Measurement of unbound drug concentrations is recommended
297 for each plasma sample only if the binding is concentration-dependent or is affected by
298 metabolites or other time-varying factors. Otherwise, the unbound fraction should be determined
299 using a limited number of samples or even a single sample from each patient. For drugs and
300 metabolites with a low extent of plasma protein binding (e.g., less than 80 percent), changes in
301 PK resulting from alterations in protein binding due to impaired renal function are generally
302 expected to be small relative to those in patients with normal renal function. In such cases, a
303 description and analysis of the PK of the drug or metabolite in terms of total concentrations is
304 sufficient.

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

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 study design can be used to determine the need for dose adjustment. The intent of a reduced study design is to represent a *worst-case* scenario, i.e., one that shows the greatest impact 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, subjects with severe renal impairment (see Table 1) can be considered to represent the worst-case scenario.[18] If a reduced pharmacokinetic study shows a clinically relevant effect on the PK of the drug in subjects with severe renal impairment, the sponsor should characterize the effect of impaired renal function on the drug's PK in subjects with the remaining levels of impaired renal function (see Table 1). If no difference in PK is observed between patients at the extremes of renal function, then no further study is recommended. Other study design considerations described in sections IV.B also apply to this setting.

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

If there is adequate representation of patients with varying degrees of renal function (see section III), 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 trials could be sufficient to characterize the impact of renal function on drug exposure for the population that was represented in the trials. If patients with severe renal impairment were not enrolled in sufficient numbers, a reduced design renal impairment study could be needed to provide appropriate dosing recommendations in labeling for the impaired renal function population not represented in clinical trials. When possible, renal function should be assessed as independent predictor of exposure-response relationships.

To allow for 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). The following are important considerations:

- Sufficient numbers of patients over a range of renal function
- Accurate records of dosing and sample collection times

[18] Zhang L, Xu N, Xiao S, Arya V, Zhao P, , Lesko LJ, Huang SM, 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.

- Adequate numbers of samples per patient

- Unbound drug concentrations when appropriate

- Active metabolite levels, where applicable, in addition to levels of the parent drug

- Use of the same measure of estimated 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 approaches, refer to the FDA draft guidance for industry entitled *Population Pharmacokinetics* (July 2019).[19]

E. Effect of Dialytic Therapies on the PK of a Drug

The primary questions to be addressed by studying the effect of dialytic therapies on the PK of a drug are: (1) whether the drug dosage should be adjusted because of dialysis; (2) if so, by how much; (3) and the timing of drug administration relative to dialysis. The results of the study also provide insight regarding the value of dialysis for the treatment of a drug overdose.

1. Intermittent Dialytic Therapies

This section mainly focuses on intermittent hemodialysis (IHD) as it is the most common dialysis method used in ESRD patients in the United States. However, some of the general study design principles described below for IHD can be applied to other modalities.

It is critical for the IHD study to include both on- and off-dialysis periods. Each subject can 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 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., not in close proximity to the end of a dialysis session).

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), and the make and model of the dialyzer used in the study to interpret study results and extrapolate to other dialysis conditions.

[19] When final, this guidance will represent the FDA's current thinking on this topic.

2. Continuous Dialytic Therapies

For critical care medications likely to be used in patients on continuous renal replacement therapy (CRRT), the findings from IHD studies might not be sufficient to derive dosing recommendations for patients using this modality. Therefore, it is important to evaluate the impact of CRRT on the PK of the drug to derive appropriate dosing recommendations. Given the practical challenges (e.g. the patient's hemodynamic stability and the difficulty in obtaining blood samples) when 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. As far as it is practicable, 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 can be the most feasible approach. If a multiple-dose assessment is possible, it can characterize the effect of CRRT as a patient's condition changes. One approach that could allow collection of information that informs dosage is to use a fixed blood flow rate (Q_B) with one or two commonly prescribed effluent flow rates (Q_E).[20] Sponsors are strongly encouraged to seek FDA's input early in the process of designing such studies.

3. Sample Collection and Data Analysis

To accurately estimate the clearance in ESRD patients undergoing IHD during the non-dialysis (or between dialysis) period, dosing 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:

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

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

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 from peripheral tissues after dialysis and characterize its implications for drug dosing.

F. Considerations for Pharmacodynamic Assessments

Whenever appropriate and feasible, pharmacodynamic assessments should be included in studies of impaired renal function. Such assessments will be important in situations where changes in renal function 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 derive appropriate dosage adjustments for patients with impaired renal function. The selection of the pharmacodynamic endpoints should be discussed with the appropriate FDA review staff.

V. DATA ANALYSIS

A. Estimating Pharmacokinetic Parameters

Plasma concentration data and urinary excretion data should be analyzed to estimate PK 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 compartmental modeling approaches to parameter estimation can be employed.

B. Modeling the Relationship Between Renal Function and Pharmacokinetic Parameters

The FDA recommends a regression approach in which estimated 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 groups. In either case, the potential for confounding due to differences in baseline covariates that can affect a drug's PK (e.g., age, gender, race, and 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 Renal Impairment

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 dosage adjustment for patients with impaired renal function. When there is a need for a different dosage recommendation in patients with impaired renal function compared to those with normal renal function, these dosage recommendations should be based on exposure-matching to a reference group with an acceptable benefit-risk profile for the drug. The reference group does not have to be limited to patients with normal renal function.[21]

There are a number of 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 final 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 below which a different dosage is recommended. It is not 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 between different estimating equations of renal function. In such situations, it is important to understand the reasons underlying the discrepant results and dosage recommendations in the labeling should address which measure or estimating equation to use.

VI. LABELING RECOMMENDATIONS

The Prescribing Information should include a summary of essential information about the effect of renal function on the PK and PD (if known) of the drug to inform the safe and effective use of the drug in patients with impaired renal function by the health care provider:

[21] This topic was discussed at an Advisory Committee Meeting convened on May 7, 2019. Please see Footnote **Error! Bookmark not defined.** for further information.

- Renal elimination of the drug and relevant metabolites

- Pharmacokinetic or pharmacodynamic changes relative to renal function and hemodialysis

- Clinical implications of these pharmacokinetic or pharmacodynamic changes

- Any recommended risk mitigation strategies in patients with renal impairment (e.g., different dosage recommendations, or monitoring recommendations)

For specific recommendations on how to incorporate use information in subjects with impaired renal function in labeling, refer to 21 CFR 201.57 and the following FDA final guidances for industry:

- *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

- *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010).

- *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011).

- *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

- *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016)