Guidance for Industry

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

DRAFT GUIDANCE

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

March 2010
Clinical Pharmacology

Revision 1

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

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Guidance for Industry[1]

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I. INTRODUCTION

This guidance is intended to assist sponsors planning to conduct studies to assess the influence of renal impairment on the pharmacokinetics of an investigational drug. It provides recommendations on when studies should be conducted to assess the influence of renal impairment on the pharmacokinetics of an investigational drug, the design of such studies, and how such studies should be carried out.

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

II. BACKGROUND

After entering the body, a drug is eliminated by excretion and/or by metabolism. Although elimination can occur through a variety of routes, most drugs are cleared by elimination of unchanged drug by the kidney and/or by metabolism in the liver and/or small intestine. If a drug is eliminated primarily through renal excretory mechanisms, impaired renal function usually alters the drug's pharmacokinetics (PK) to an extent that the dosage regimen needs to be changed from that used in patients with normal renal function. The most obvious type of

[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.

change arising from renal impairment is a decrease in renal excretion of a drug or its metabolites, but changes in renal metabolism can also occur. Renal impairment can adversely affect some pathways of hepatic/gut drug metabolism and has also been associated with other changes, such as changes in absorption, plasma protein binding, transport, and tissue distribution. These changes may be particularly prominent in patients with severely impaired renal function and have been observed even when the renal route is not the primary route of elimination of a drug. Thus, for most drugs that are likely to be administered to patients with renal impairment, including drugs that are not primarily excreted by the kidney, PK should be assessed in patients with renal impairment to provide appropriate dosing recommendations, with the exceptions described in section III.B.

This guidance makes recommendations regarding the following:

- When studies of PK in patients with impaired renal function should be performed and when they may be unnecessary
- The design and conduct of PK studies in patients with impaired renal function
- The design and conduct of PK studies in end-stage renal disease (ESRD) patients undergoing dialysis (e.g., hemodialysis)
- The analysis and reporting of the results of such studies
- Representation of these results in the approved product labeling

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

A. When Studies May Be Important

A PK study should be conducted in patients with impaired renal function when the drug is likely to be used in such patients and when renal impairment is likely to mechanistically alter the PK of the drug and/or its active metabolites. This would most obviously be the case if the drug or a principal active metabolite is substantially eliminated renally (i.e., if the fraction of dose excreted unchanged in the urine is at least 30%), but it can also be the case if a drug is primarily metabolized or secreted in bile, because renal impairment can inhibit some pathways of hepatic and gut drug metabolism and transport. Therefore, a PK study in patients with renal impairment should be conducted for most drugs intended for chronic use. Some drugs that are not chronically used can also be evaluated in patients with renal impairment for dose adjustment purposes if there are clinical concerns for use in these patients. Antibiotic drugs represent such a case.

Although there are limited data on the effect of renal impairment on the disposition of therapeutic proteins, data from biologics license application (BLA) reviews indicate that renal impairment has

decreased the renal clearance of cytokines or cytokine modulators that have a molecular weight less than 69 kDa. In some cases, a dose adjustment was necessary to reduce the risk of exposure-related toxicity in patients with renal impairment (e.g., anakinra, peginterferon alfa-2A, peginterferon alfa-2B, and oprelvekin). Therefore, renal impairment studies are recommended for this class of therapeutic proteins during their development.

In addition, for ESRD patients undergoing dialysis, PK should be studied under both dialysis and non-dialysis conditions to determine the extent to which dialysis contributes to the elimination of the drug and potentially active metabolites (see section IV.C).

B. When Studies May Not Be Important or Practical

For some drugs, renal impairment is not likely to alter PK enough to justify dosage adjustment. In such cases, a study to confirm that prediction may be helpful, but is not necessary. If a study is not conducted, the labeling should indicate that the impact of renal impairment was not studied, but that an effect requiring dosage adjustment is unlikely to be present. Current knowledge suggests that the following drug properties may justify this approach:

- Gaseous or volatile drug and active metabolites that are primarily eliminated through the lungs

- Drugs intended only for single-dose administration unless clinical concerns dictate otherwise

- Monoclonal antibodies

C. Other Considerations

Even when renal impairment is likely to have little or no effect on a drug's PK, the impact of dialysis on the PK of a drug should be considered. Patients on dialysis may require greater doses of certain drugs than patients with normal renal function. This is discussed further in the following section.

IV. STUDY DESIGN

The safety and efficacy of a drug are generally established for a particular dosage regimen (or range of dosage regimens) in late phase (phase 3) clinical trials involving relatively typical representatives from the target patient population. Frequently, individuals with significantly impaired renal function are explicitly ***excluded*** from participation in these studies. However, there may be a sufficient range of renal function to allow an estimation of the effects of decreased renal function from population PK analysis. The primary goal of the recommended study in patients with impaired renal function is to determine whether the PK

is altered to such an extent that the dosage should be adjusted from the dose(s) established in the phase 3 trials.

In many cases the effects of impaired renal function on drug PK can be evaluated initially with a "reduced PK study" design (see IV.A below), essentially a "worst case" study in patients with little or no renal function. This approach would be used for drugs that are predominantly metabolized or secreted in the bile. The reduced PK study design compares PK in patients at the extremes of renal function (i.e., patients with normal renal function and patients with ESRD not yet on dialysis). If a reduced PK study shows a substantial effect (e.g., at least a 50-100% increase in AUC, or a lesser effect if the drug has a narrow therapeutic range) in the renal impairment patients, a "full" renal impairment study in patients with all intermediate levels of renal functional impairment ("full study design," see IV.B below) should be conducted. If no difference in PK is seen between patients at the extremes of renal function, no further study needs to be undertaken. Appendix 1 includes a model for determining when a renal impairment study is recommended.

A. Reduced PK Study Design

1. Study Participants

The reduced PK study compares the PK parameters in ESRD patients not yet on dialysis with PK in subjects with normal renal function. The number of ESRD patients enrolled in the study should be sufficient to determine whether PK in ESRD patients is meaningfully different from patients with normal renal function. If results from the initial study in ESRD patients show a substantial PK difference from normal subjects ("positive" in Appendix 1) that would warrant dose adjustment in patients with renal impairment, a full PK study should be carried out (see IV.B below).

The control renal function group in this study ideally should be representative of a typical patient population (with "normal" renal function) for the drug to be studied. For example, it should not consist of normal healthy young male volunteers if the typical patient population is composed of older subjects and includes women. A suitable control group for a drug intended for treatment of Alzheimer's disease, for example, would be otherwise healthy elderly male and female patients. Their baseline renal function would clearly not be similar to that of young healthy male volunteers.

2. Drug Administration

A single-dose study is satisfactory for cases where there is clear prior evidence that single-dose studies accurately describe the PK for the pertinent drug and potentially active metabolites. This will be true when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the patients to be studied. A multiple-dose study is usually recommended when the drug or an active metabolite exhibits nonlinear or time-dependent PK.

In single-dose studies, the same dose can generally be administered to all patients in the study regardless of renal function, because the peak concentration generally is not substantially affected by renal function. In multiple-dose studies, lower or less frequent dosing may be important to consider in patients with impaired renal function to prevent accumulation of drug and metabolites. The dosage regimen can be adjusted based on the best available pre-study estimates of the PK of the drug and its active metabolites in patients with impaired renal function. In multiple-dose studies, the dosing should usually be continued long enough to achieve steady state. A loading dose strategy may be desirable to facilitate the process of reaching steady state, particularly if the elimination half-life is greatly prolonged in patients with renal impairment.

3. Sample Collection and Analysis

Plasma or whole blood, if appropriate, and urine samples should be analyzed for parent drug and any metabolites with known or suspected activity (therapeutic or adverse). 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 active drugs and metabolites, the unbound concentrations are generally believed to determine the rate and extent of delivery to the sites of action. Unbound concentrations should be measured in each plasma sample only if the binding is concentration-dependent and/or is affected by metabolites or other time-varying factors. Otherwise, the fraction unbound may be determined using a limited number of samples or even a single sample from each patient. For drugs and metabolites with a relatively low extent of plasma protein binding (e.g., extent of binding less than 80%), alterations in binding due to impaired renal function are small in relative terms. In such cases, description and analysis of the PK in terms of total concentrations should be sufficient.

4. Additional Studies

If the results from the initial "reduced" study in ESRD patients are positive (that is, if clinically significant PK changes are observed), further studies to assess the impact of intermediate decreases in creatinine clearance or estimated glomerular filtration rate (eGFR) on the PK of the drug can be conducted. A full study could be carried out (see IV.B), or additional studies such as a population PK evaluation in phase 2 or phase 3 clinical trials can be conducted (see the decision tree in Appendix 1). Typically in population PK studies, each patient should be only sparsely sampled to obtain plasma drug concentration data. Techniques such as nonlinear mixed effects modeling may be used to model the relationship between the various covariates, such as creatinine clearance and PK parameters describing the apparent clearance of the drug (CL/F where CL is the apparent clearance, calculated as dose/AUC and F is the oral bioavailability).

In principle, such a population PK study design and analysis should retain some of the critical components of the more conventional studies described in the following section on full study design. The following are important considerations:

- Inclusion of a sufficient number of subjects and a sufficient representation of a range of renal function to allow the study to detect PK differences large enough to warrant dosage adjustment

- Measurement of unbound concentrations when appropriate

- Measurement of potentially active metabolites as well as parent drug

Such features are particularly critical if the sponsor intends to use the results to support a claim that no dosage adjustment is required for patients with impaired renal function.

B. Full PK Study Design

1. Study Participants and Measures of Renal Impairment

The control renal function group in this study should be the same as that used in the reduced PK study. In instances where enrollment of subjects with the condition for which the drug is indicated may not be appropriate, or if enrollment of enough subjects with varying degrees of renal impairment may be difficult, an alternative is to use volunteers who are comparable to the typical patient population with respect to renal function and other factors such as age, gender, race, and weight.

In assessing the impact of renal impairment on PK, there are several ways to define renal function. Although exogenous markers such as inulin, iothalamate, EDTA, diethylene triamine pentaacetic acid, and iohexol provide accurate estimation of glomerular filtration rate (GFR), these methods are not routinely used in clinical practice.

There are two commonly used serum-creatinine based equations used to estimate renal function:

(1) Estimated creatinine clearance (Clcr) by the Cockcroft-Gault (C-G) equation

CLcr in mL/min is estimated from a spot serum creatinine (mg/dL) determination using the following formula:

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ \ for\ \ female\ patients\}$$

(2) Estimated glomerular filtration rate (eGFR) from the Modification of Diet in Renal Disease (MDRD) Study

Several versions of MDRD equations have been created in recent years and future modifications are anticipated (e.g., corrections for Asian ethnic groups). One example is listed below.

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = \mathbf{175} \times (S_{cr,\,std})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Scr, std: serum creatinine measured with a standardized assay.

Table 1. Classification of Renal Function Based on Estimated GFR (eGFR) or Estimated Creatinine Clearance (CLcr)[a]

Stage	Description[b]	eGFR[c] (mL/min/1.73m^2)	CLcr[d] (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60-89	60-89
3	Moderate decrease in GFR	30-59	30-59
4	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis Requiring dialysis	<15 not on dialysis Requiring dialysis

[a] In some situations, collection of 24-hour urine samples for measurement of creatinine clearance, or measurement of clearance of an exogenous filtration marker, may provide better estimates of GFR than the prediction equations. The situations include determination of GFR for patients in the following scenarios: undergoing kidney replacement therapy; acute renal failure; extremes of age, body size, or muscle mass; conditions of severe malnutrition or obesity; disease of skeletal muscle; or on a vegetarian diet.

[b] Stages of renal impairment are based on *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation* in 2002; GFR: glomerular filtration rate;

[c] eGFR: estimate of GFR based on an MDRD equation;

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

Historically, the C-G equation has been widely used in PK studies, and it is used commonly in the application of drug dosing guidance for patients with impaired renal function. Recently, the modification of diet in renal disease (MDRD) eGFR equation has increasingly been used as the standard in clinical use to assess renal function. A movement to standardize the serum creatinine assays is currently under way. Either the C-G or MDRD equation can be used to assign subjects to a renal impairment group or stage, and PK results should be shown for both C-G estimates of creatinine clearance and eGFR. Creatinine clearance calculated using timed urine collections (e.g., 24 hours) is not suitable for routine clinical practice or clinical trials and in many settings does not improve estimates of GFR over that provided by prediction equations. In addition to collection errors, diurnal variation in GFR and day-to-day variation in creatinine excretion may also contribute to the errors for GFR estimation with timed urine collection. Important exceptions may be the estimation of GFR in individuals with variation in dietary intake (vegetarian diet, creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting), because these factors are not specifically taken into account in prediction equations. In these situations, collection of a 24-hour urine sample for measurement of creatinine clearance, or measurement of clearance of

an exogenous filtration marker, may provide better estimates of GFR than prediction equations. Using other measures of renal function that can characterize differentially glomerular filtration or renal tubular secretion may provide an additional mechanistic understanding of the effect of renal impairment on PK, especially for drugs that are anticipated to show a wide variation in PK from preclinical or early human studies or drugs that have a narrow therapeutic range. These methods are encouraged as useful additions, but not as alternatives to creatinine clearance or eGFR estimates.

In general, individuals with decreased eGFR in the range of 60 to 89 mL/min/1.73 m^2 without kidney damage are not at an increased risk for adverse outcomes from drugs that are renally excreted. For drugs with reasonably wide therapeutic range, subjects may be stratified based on ≥ 60 /min/1.73 m^2 (relatively normal), 15-59 /min/1.73 m^2 (moderate to severe renal damage), and ≤ 15 mL/min/1.73 m^2 (end stage) without dialysis, and requiring dialysis, when using eGFR to stage renal function or the approximately equivalent groups based on C-G creatinine clearance.

To ensure adequate representation of subjects with various degrees of renal impairment, approximately equal numbers of control subjects and subjects with various levels of impaired renal function should be enrolled in Stages 1-5 (see Table 1 above). The subjects in these groups should be comparable to each other with respect to age, gender, race, and weight. Other factors with significant potential to affect the PK of the drug to be studied (e.g., diet, smoking, alcohol intake, concomitant medications, race/ethnicity) should be considered, depending on the drug. The number of subjects enrolled in each group should be sufficient to detect the level of renal impairment at which the PK may be changed sufficiently to warrant dose adjustment. The PK variability within the subject group, as well as the PK/pharmacodynamic (PD) relationships for both therapeutic and adverse responses (therapeutic range), will affect this decision.

In pediatric subjects, a measured creatinine clearance or a measurement of the elimination of an exogenous substrate such as iohexol as an estimate of the glomerular filtration rate (GFR) is appropriate. For larger efficacy or population PK studies where an estimate of GFR is important, the modified Schwartz equation, with adjustments for premature infants, neonates, children, and adolescent males, can be used (Schwartz, G.J. 2007). The older Schwartz equations must be corrected for the newer enzymatic creatinine assays. Newer formulas incorporating cystatin C may be used to estimate GFR in pediatric patients with impaired renal function (Schwartz, G.J. 2009) (also refer to the draft guidance for industry on *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*[2]).

2. Drug Administration

[2] This draft guidance is being referenced for completeness only. As a draft document, it is not intended to be implemented until published in final form.

Considerations regarding drug administration are the same as in the reduced PK study.

3. Sample Collection and Analysis

See the reduced PK study section on Sample Collection and Analysis.

C. Effect of Dialysis on Pharmacokinetics

Dialysis may affect the PK of a drug to an extent that dosage adjustment is needed. The need for dosage adjustment arises when a significant fraction of the drug or active metabolites is removed by the dialysis process. In such cases, a change in the dosage regimen, such as a supplemental dose following the dialysis procedure, may be appropriate.

For drugs that are likely to be administered to ESRD patients treated with dialysis, PK should be studied in such patients under both dialysis and non-dialysis (between dialysis) conditions to determine the extent to which dialysis contributes to the elimination of the drug and potentially active metabolites. Primary questions to be addressed are whether the dosage should be adjusted as a consequence of dialysis and, if so, by how much. The results of the study also provide insight regarding the value of dialysis for treatment of overdose.

In general, a study of the effect of dialysis on PK may be omitted if the dialysis procedure is unlikely to result in significant elimination of drug or active metabolites. This is generally true for drugs that have a large molecular weight or that have a tight binding to plasma proteins not affected by impaired renal function. It is also usually true when drugs and active metabolites have a large volume of distribution or are primarily nonrenally cleared. If the drug and metabolites have a large volume of distribution, only a small fraction of the amount in the body will be removed by dialysis. For example, if the volume of distribution is greater than 360 L, less than 10 percent of the amount initially in the body could be removed by 3 hours of high-flux hemodialysis with an unbound dialysis clearance of 200 mL/min. If the drug and metabolites have primarily nonrenal clearance, dialysis contributes a relatively small amount to the overall clearance. For example, if nonrenal clearance is greater than 125 mL/min, 3 hours of high-flux hemodialysis with a dialysis clearance of 200 mL/min administered every 2 days would contribute less than 10 percent to the overall elimination.

1. Study Design

As it is the most common dialysis method used in chronic ESRD patients, intermittent hemodialysis (HD) is usually the most important method to be evaluated. Because most dialysis centers in the United States are currently using a high-flux dialyzer during the intermittent HD, PK studies are recommended in patients treated with high-flux HD. The dialysis study (or studies) should include both non-dialysis (between dialysis) and dialysis periods. The blood flow, dialysate flow, and the make and model of the dialyzer should be recorded. If the dialyzer permeability coefficient-surface area product (P·S) is measured using a reference substance such as creatinine, it may be

possible to transfer results between different dialyzers using the equation developed by Renkin for analysis of in vitro dialysis clearance (CL_D):

$$CL_D = Q\left(1 - e^{-P \cdot S/Q}\right)$$ Where Q is dialyzer blood flow.

PK studies should also be considered in peritoneal dialysis if the drug is likely to be used in these patients and the peritoneal dialysis is likely to significantly affect the drug PK.

For patients with acute renal failure treated with continuous renal replacement therapy (CRRT) rather than intermittent HD, drug deposition may be different from HD. It may be difficult to directly extrapolate the effect of intermittent HD on the PK of drugs to CRRT. The in vitro data and/or the filter clearance rate (calculated from the actual amount of drug removed) plus the available data from intermittent HD may make it possible to estimate appropriate dosing recommendations in these patients until PK data in CRRT patients from definitive clinical studies are available.

2. Sample Collection and Data Analysis

To accurately estimate the clearance in ESRD patients during the non-dialysis (or between dialysis) period, dosing and sampling time should be carefully planned to capture the full PK profile of the drug and its active metabolites. To determine the clearance during dialysis, blood samples should be collected pre-dialysis and from blood flowing from both the arterial and venous sides of the dialyzer at appropriate intervals during the dialysis period. The entire dialysate should be collected, its volume recorded, and a sample retained for drug concentration analysis. Blood flow, dialysate flow during the dialysis, and the make and model of the dialyzer should be recorded.

Plasma (or blood if this is the reference for previous PK studies) concentrations of the drug and its active metabolites (if any) should be measured in blood (entering the dialyzer) and dialysate samples. The total amount of drug removed in the dialysate should be determined and dialysis clearance (CL_D) can be calculated from the following equation:

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

where t_0 marks the start time and t_1 the termination of the hemodialysis session.

Pre-dialysis and end-of-dialysis blood samples 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 in order to assess the need for administering

supplemental drug doses to hemodialysis patients.

D. Pharmacodynamic Assessments

Whenever appropriate, pharmacodynamic assessment should be included in the studies of renal impairment. The selection of the pharmacodynamic endpoints should be discussed with the appropriate FDA review staff and should be based on the pharmacological characteristics of the drug and metabolites (e.g., extent of protein binding, therapeutic range, and the behavior of other drugs in the same class in patients with renal impairment).

V. DATA ANALYSIS

The primary intent of the data analysis is to assess whether dosage adjustment is required for patients with impaired renal function and, if so, to develop dosing recommendations for such patients based on measures of renal function. The data analysis typically consists of the following steps:

- Estimation of PK parameters
- Mathematical modeling of the relationship between measures of renal function and the PK parameters
- Development of dosing recommendations, including an assessment of whether dosage adjustment is warranted in patients with impaired renal function

A. Parameter Estimation

Plasma concentration data and urinary excretion data should be analyzed to estimate various parameters describing the PK of the drug and its active metabolites. In addition to CL_D, measured PK parameters can include the area under the plasma concentration-time curve (AUC), peak concentration (C_{max}), 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 ($t_{1/2}$). If CL and CL_{NR} are not estimated directly, indirect estimates can be made from absolute bioavailability studies. The PK parameters of active metabolites can include the AUC, peak concentration (C_{max}), renal clearance (CL_R), and terminal half-life ($t_{1/2}$). Non-compartmental and/or compartmental modeling approaches to parameter estimation can be employed.

B. Modeling the Relationship Between Renal Function and PK

The objective of this step is to construct mathematical models for the relationships between estimated renal function (e.g., creatinine clearance (CL_{CR}) or eGFR), and relevant PK

parameters. The intended result is a model that can successfully predict PK behavior given information about renal function. Generally, this involves a regression approach in which estimated renal function and the PK parameters are treated as continuous variables. This is usually preferred to an analysis in which CL_{CR} or eGFR is treated as a categorical variable corresponding to the normal, mild, moderate, and severe renal impairment groups.

The intent of the modeling procedure is to provide a rational quantitative basis for dosage recommendations in the drug's labeling. The model itself may be described in the clinical pharmacology section of the labeling.

The reported modeling results should include estimates of the parameters of the chosen model as well as measures of their precision (standard errors or confidence intervals). Prediction error estimates are also desirable (e.g., confidence bounds for prediction of clearance for the drug and its active metabolites over a range of CL_{CR} or eGFR).

C. Development of Dosing Recommendations

Specific dosing recommendations should be constructed based on the study results using the aforementioned model for the relationships between creatinine clearance or eGFR and relevant PK parameters. Typically the dose, dosing interval, or both are adjusted to produce a range of plasma concentrations of drug or active metabolites that is similar in subjects with normal renal function and subjects with impaired renal function. Simulations are encouraged as a means to identify doses and dosing intervals that achieve that goal for subjects with different levels of renal function. Nomograms will help in providing dose recommendations and can lead to more precise dosing for drugs with a narrow therapeutic range.

For some drugs, such as drugs eliminated primarily by metabolism or biliary secretion, even severe renal impairment may not alter PK sufficiently to warrant dosage adjustment. A sponsor could support this conclusion by providing an analysis of the study data to show that the PK measurements most relevant to therapeutic outcome in patients with severe renal impairment are similar to those in patients with normal renal function.

VI. LABELING

The labeling should reflect the clinically relevant information pertaining to the effect of renal function on the pharmacokinetics and pharmacodynamics (if known) of the drug. General suggestions on the content of applicable labeling sections follow.

A. Highlights of Prescribing Information (Highlights)

It may be appropriate to include in the Highlights a concise summary of information detailed in other sections of the Full Prescribing Information (e.g., Dosage and Administration,

Contraindications, Warnings and Precautions, Use in Specific Populations) about use in patients with renal impairment based on the type and clinical relevance of the information.

B. Dosage and Administration

For many drugs, patients with impaired renal function may require dosing adjustments. In such cases, the following information should be included:

- If there is a need for dosage adjustment in patients with renal impairment, it should be noted and the adjustments described, either globally (reduce by 50% in patients with moderate renal impairment (creatinine clearance of 30-59 mL/min as estimated by Cockcroft-Gault or eGFR of 30-59 mL/min/1.73 m^2 as estimated by MDRD)) or in detail, as the following table illustrates.

Table 2. An Example of Dosing Recommendation in Various Renal Function Groups Based on Estimated GFR (eGFR) or Estimated Creatinine Clearance (CLcr)

Stage	Description[a]	eGFR[b] (mL/min/ 1.73m^2)	Dose (mg)	Frequency	CLcr[c] (mL/min)	Dose (mg)	Frequency
1	Control (normal) GFR	≥ 90	200	Every 12 hours	≥ 90	200	Every 12 hours
2	Mild decrease in GFR	60-89	200	Every 12 hours	60-89	200	Every 12 hours
3	Moderate decrease in GFR	30-59	100	Every 12 hours	30-59	100	Every 12 hours
4	Severe decrease in GFR	15-29	100	Every 24 hours	15-29	100	Every 24 hours
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	50	Every 24 hours	<15 not on dialysis	50	Every 24 hours
		Requiring dialysis		Supplemental dose, if appropriate, should be given after dialysis[d]	Requiring dialysis		Supplemental dose, if appropriate, should be given after dialysis[d]

[a] Stages of renal impairment are based on *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation* in 2002; GFR: glomerular filtration rate;
[b] eGFR: estimate of GFR based on MDRD equation;
[c] Clcr: estimated creatinine clearance based on the C-G equation;
[d] The need for supplemental dose is dependent on the drug dialyzability.

- Special consideration should be given to combination drug products. If adjusting the individual components of a combination product is impossible because each component is differentially affected by decreased renal function, and the available combinations do not allow appropriate adjustment, use of the combination in patients with decreased renal function should be discouraged.

C. Contraindications and Warnings and Precautions

If renal impairment results in changes in drug pharmacokinetics that make the drug unsafe for use in patients with renal impairment, this information should be included in the Contraindications section. Serious concerns that might nonetheless allow for use should be noted in the Warnings and Precautions section with a cross reference to the Dosage and Administration section, as appropriate.

D. Use in Specific Populations

A subsection in the Use in Specific Populations section may be included (e.g., "Renal Impairment") to briefly describe clinically relevant information about patients with renal impairment. For example, a concise summary of the clinical implications of differences in response or recommendations for use of the drug in patients with renal impairment should be included in this subsection, with a reference to the Dosage and Administration, Contraindications, Warnings and Precautions, and Clinical Pharmacology sections, as appropriate, for more detailed information.

E. Overdosage

Although the primary objective of a hemodialysis study is to evaluate the need for dosing adjustments in ESRD, additional information regarding the value of hemodialysis in overdose situations may reasonably be garnered from the results of such studies. In situations in which this information is known, the Overdosage section could note the extent of elimination by hemodialysis and whether hemodialysis is (or is not) known to be useful in treating an overdose.

F. Clinical Pharmacology

In general, the more detailed study results from renal impairment studies should be presented in the pharmacokinetics subsection of the Clinical Pharmacology section, with the clinical implications described in Use in Specific Populations and, where appropriate, Dosage and Administration, Contraindications, or Warnings and Precautions. The pharmacokinetics subsection should include information on the following, when appropriate and applicable:

- Mechanism of renal elimination (e.g., filtration, active secretion, or re-absorption) and transporters that may be involved

- Percentage of drug eliminated by renal excretion and whether it is eliminated unchanged or as metabolites

- Results of studies comparing PK in normal subjects and subjects with varying degrees of renal impairment (i.e., the studies described in IV.A and IV.B) and methods used to stratify the subjects

- Disposition of metabolites in patients with impaired renal function (if applicable)

    - Effects of renal impairment on protein binding of parent drug and metabolites (if applicable)

    - Effects of changes in urinary pH or other special situations that should be mentioned (e.g., tubular secretion inhibited by probenecid), if applicable

    - Effects of impaired renal function on stereospecific disposition of enantiomers of a racemic drug product, if there is evidence of differential stereoisomeric activity or toxicity, as applicable

588 **Appendix 1. Decision Tree for Determining When a Renal**
589 **Impairment Study Should Be Conducted**
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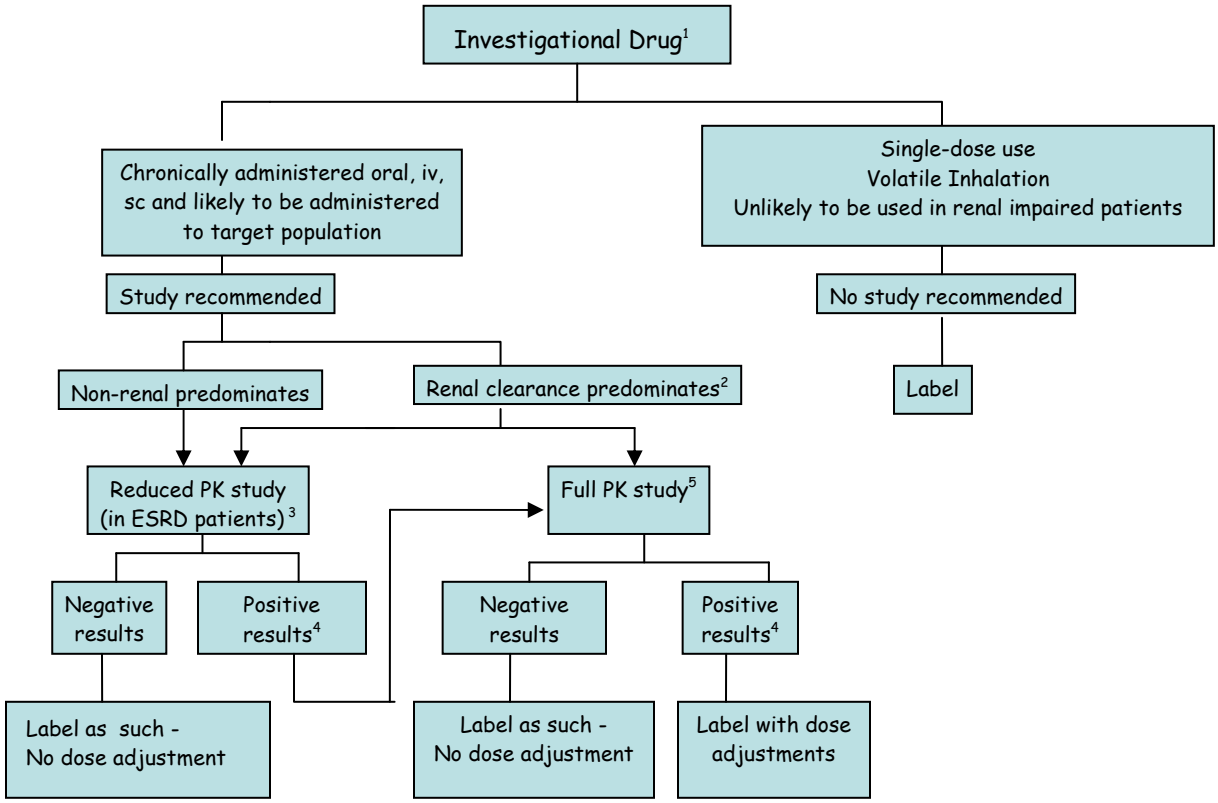

1. Metabolites (active/toxic) follow the same decision tree.
2. The sponsor has the option of conducting a reduced study in ESRD patients or a full study.
3. To be conducted in ESRD patients not yet on dialysis
4. The results are "positive" when the PK changes are clinically significant based on exposure-response of the drug
5. See section IV.B for the full PK study design, or additional studies can be conducted including a population PK evaluation

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593 Note that there may be situations when renal impairment studies are recommended for single-dose use, if
594 clinical concerns dictate the need. Examples include antibiotics. Renal impairment studies are also
595 recommended for therapeutic proteins that are cytokine or cytokine modulators with a molecular weight
596 less than 69 KDa.
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602 **REFERENCES**
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