
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DRAFT GUIDANCE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
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Center for Drug Evaluation and Research (CDER)

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Revision 1

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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND.....	1
III.	DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED RENAL FUNCTION.....	2
	A. WHEN STUDIES MAY BE IMPORTANT	2
	B. WHEN STUDIES MAY NOT BE IMPORTANT OR PRACTICAL	3
	C. OTHER CONSIDERATIONS.....	3
IV.	STUDY DESIGN.....	3
	A. REDUCED PK STUDY DESIGN	4
	B. FULL PK STUDY DESIGN	6
	C. EFFECT OF DIALYSIS ON PHARMACOKINETICS	10
	D. PHARMACODYNAMIC ASSESSMENTS.....	12
V.	DATA ANALYSIS.....	12
	A. PARAMETER ESTIMATION	12
	B. MODELING THE RELATIONSHIP BETWEEN RENAL FUNCTION AND PK.....	12
	C. DEVELOPMENT OF DOSING RECOMMENDATIONS.....	13
VI.	LABELING	13
	A. HIGHLIGHTS OF PRESCRIBING INFORMATION (HIGHLIGHTS).....	13
	B. DOSAGE AND ADMINISTRATION.....	14
	C. CONTRAINDICATIONS AND WARNINGS AND PRECAUTIONS.....	15
	D. USE IN SPECIFIC POPULATIONS	15
	E. OVERDOSAGE	16
	F. CLINICAL PHARMACOLOGY	16
	APPENDIX 1 DECISION TREE FOR DETERMINING WHEN A RENAL.....	17
	IMPAIRMENT STUDY SHOULD BE CONDUCTED.....	17
	REFERENCES.....	17

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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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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.

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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.

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

51

52 This guidance makes recommendations regarding the following:

53

54 • When studies of PK in patients with impaired renal function should be performed and
55 when they may be unnecessary

56

57 • The design and conduct of PK studies in patients with impaired renal function

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59 • The design and conduct of PK studies in end-stage renal disease (ESRD) patients
60 undergoing dialysis (e.g., hemodialysis)

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62 • The analysis and reporting of the results of such studies

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64 • Representation of these results in the approved product labeling

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66

67 III. DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED 68 RENAL FUNCTION

69

70 A. When Studies May Be Important

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

82

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

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85 decreased the renal clearance of cytokines or cytokine modulators that have a molecular weight less
86 than 69 kDa. In some cases, a dose adjustment was necessary to reduce the risk of exposure-related
87 toxicity in patients with renal impairment (e.g., anakinra, peginterferon alfa-2A, peginterferon alfa-
88 2B, and oprelvekin). Therefore, renal impairment studies are recommended for this class of
89 therapeutic proteins during their development.

90

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

94

B. When Studies May Not Be Important or Practical

96

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

103

- 104 • Gaseous or volatile drug and active metabolites that are primarily eliminated through the
105 lungs
- 106
- 107 • Drugs intended only for single-dose administration unless clinical concerns dictate
108 otherwise
- 109
- 110 • Monoclonal antibodies

111

C. Other Considerations

113

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

118

119

IV. STUDY DESIGN

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

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

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

143

A. Reduced PK Study Design

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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).

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2. Drug Administration

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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.

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171
172 In single-dose studies, the same dose can generally be administered to all patients in the
173 study regardless of renal function, because the peak concentration generally is not
174 substantially affected by renal function. In multiple-dose studies, lower or less frequent
175 dosing may be important to consider in patients with impaired renal function to prevent
176 accumulation of drug and metabolites. The dosage regimen can be adjusted based on
177 the best available pre-study estimates of the PK of the drug and its active metabolites in
178 patients with impaired renal function. In multiple-dose studies, the dosing should
179 usually be continued long enough to achieve steady state. A loading dose strategy may
180 be desirable to facilitate the process of reaching steady state, particularly if the
181 elimination half-life is greatly prolonged in patients with renal impairment.

182 183 3. *Sample Collection and Analysis*

184
185 Plasma or whole blood, if appropriate, and urine samples should be analyzed for parent
186 drug and any metabolites with known or suspected activity (therapeutic or adverse).
187 The frequency and duration of plasma sampling and urine collection should be
188 sufficient to accurately estimate the relevant pharmacokinetic parameters for the parent
189 drug and its active metabolites (see section V, Data Analysis).

190 Plasma protein binding is often altered in patients with impaired renal function. For
191 systemically active drugs and metabolites, the unbound concentrations are generally
192 believed to determine the rate and extent of delivery to the sites of action. Unbound
193 concentrations should be measured in each plasma sample only if the binding is
194 concentration-dependent and/or is affected by metabolites or other time-varying factors.
195 Otherwise, the fraction unbound may be determined using a limited number of samples
196 or even a single sample from each patient. For drugs and metabolites with a relatively
197 low extent of plasma protein binding (e.g., extent of binding less than 80%), alterations
198 in binding due to impaired renal function are small in relative terms. In such cases,
199 description and analysis of the PK in terms of total concentrations should be sufficient.

200 201 4. *Additional Studies*

202
203 If the results from the initial “reduced” study in ESRD patients are positive (that is, if
204 clinically significant PK changes are observed), further studies to assess the impact of
205 intermediate decreases in creatinine clearance or estimated glomerular filtration rate
206 (eGFR) on the PK of the drug can be conducted. A full study could be carried out (see
207 IV.B), or additional studies such as a population PK evaluation in phase 2 or phase 3
208 clinical trials can be conducted (see the decision tree in Appendix 1). Typically in
209 population PK studies, each patient should be only sparsely sampled to obtain plasma
210 drug concentration data. Techniques such as nonlinear mixed effects modeling may be
211 used to model the relationship between the various covariates, such as creatinine
212 clearance and PK parameters describing the apparent clearance of the drug (CL/F where
213 CL is the apparent clearance, calculated as $dose/AUC$ and F is the oral bioavailability).

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214 In principle, such a population PK study design and analysis should retain some of the
215 critical components of the more conventional studies described in the following section
216 on full study design. The following are important considerations:
217

- 218 • Inclusion of a sufficient number of subjects and a sufficient representation of a
219 range of renal function to allow the study to detect PK differences large enough to
220 warrant dosage adjustment
- 221
- 222 • Measurement of unbound concentrations when appropriate
- 223
- 224 • Measurement of potentially active metabolites as well as parent drug
- 225

226 Such features are particularly critical if the sponsor intends to use the results to support
227 a claim that no dosage adjustment is required for patients with impaired renal function.
228

229 **B. Full PK Study Design**

230 *1. Study Participants and Measures of Renal Impairment*

231
232 The control renal function group in this study should be the same as that used in the
233 reduced PK study. In instances where enrollment of subjects with the condition for
234 which the drug is indicated may not be appropriate, or if enrollment of enough subjects
235 with varying degrees of renal impairment may be difficult, an alternative is to use
236 volunteers who are comparable to the typical patient population with respect to renal
237 function and other factors such as age, gender, race, and weight.
238

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

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

246 (1) Estimated creatinine clearance (Cl_{cr}) by the Cockcroft-Gault (C-G) equation

247
248 *Cl_{cr} in mL/min is estimated from a spot serum creatinine (mg/dL) determination*
249 *using the following formula:*

$$250 \quad Cl_{cr} \text{ (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}} \{ \times 0.85 \text{ for female patients} \}$$

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

254
255 Several versions of MDRD equations have been created in recent years and future
256 modifications are anticipated (e.g., corrections for Asian ethnic groups). One example
257 is listed below.

258
259
$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{S}_{\text{cr, std}})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times$$

260 (1.212 if African American)

261
262 Scr, std: serum creatinine measured with a standardized assay.

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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	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

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^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.

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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

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

302 In general, individuals with decreased eGFR in the range of 60 to 89 mL/min/1.73 m²
303 without kidney damage are not at an increased risk for adverse outcomes from drugs
304 that are renally excreted. For drugs with reasonably wide therapeutic range, subjects
305 may be stratified based on ≥ 60 /min/1.73 m² (relatively normal), 15-59 /min/1.73 m²
306 (moderate to severe renal damage), and ≤ 15 mL/min/1.73 m² (end stage) without
307 dialysis, and requiring dialysis, when using eGFR to stage renal function or the
308 approximately equivalent groups based on C-G creatinine clearance.
309

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

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

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332 2. *Drug Administration*
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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.

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

335

336 3. *Sample Collection and Analysis*

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

339

C. Effect of Dialysis on Pharmacokinetics

341

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

346

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

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

366

367 1. *Study Design*

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

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

379
380
$$CL_D = Q(1 - e^{-P.S/Q})$$
 Where Q is dialyzer blood flow.

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

384
385 For patients with acute renal failure treated with continuous renal replacement therapy
386 (CRRT) rather than intermittent HD, drug deposition may be different from HD. It may
387 be difficult to directly extrapolate the effect of intermittent HD on the PK of drugs to
388 CRRT. The in vitro data and/or the filter clearance rate (calculated from the actual
389 amount of drug removed) plus the available data from intermittent HD may make it
390 possible to estimate appropriate dosing recommendations in these patients until PK data
391 in CRRT patients from definitive clinical studies are available.

392
393 **2. *Sample Collection and Data Analysis***

394
395 To accurately estimate the clearance in ESRD patients during the non-dialysis (or
396 between dialysis) period, dosing and sampling time should be carefully planned to
397 capture the full PK profile of the drug and its active metabolites. To determine the
398 clearance during dialysis, blood samples should be collected pre-dialysis and from
399 blood flowing from both the arterial and venous sides of the dialyzer at appropriate
400 intervals during the dialysis period. The entire dialysate should be collected, its volume
401 recorded, and a sample retained for drug concentration analysis. Blood flow, dialysate
402 flow during the dialysis, and the make and model of the dialyzer should be recorded.

403
404 Plasma (or blood if this is the reference for previous PK studies) concentrations of the
405 drug and its active metabolites (if any) should be measured in blood (entering the
406 dialyzer) and dialysate samples. The total amount of drug removed in the dialysate
407 should be determined and dialysis clearance (CL_D) can be calculated from the following
408 equation:

409
410
411
$$CL_D = \frac{\text{Amount Recovered}}{AUC_{t_0 - t_1}}$$

412
413 where t_0 marks the start time and t_1 the termination of the hemodialysis session.

414
415 Pre-dialysis and end-of-dialysis blood samples should also be used to measure drug
416 binding to plasma proteins. The fraction of the administered dose that is recovered in
417 the dialysate should be calculated in order to assess the need for administering

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418 supplemental drug doses to hemodialysis patients.

419

420 **D. Pharmacodynamic Assessments**

421

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

427

428

429 **V. DATA ANALYSIS**

430

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

435

436 • Estimation of PK parameters

437

438 • Mathematical modeling of the relationship between measures of renal function and the
439 PK parameters

440

441 • Development of dosing recommendations, including an assessment of whether dosage
442 adjustment is warranted in patients with impaired renal function

443

444 **A. Parameter Estimation**

445

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

456

457 **B. Modeling the Relationship Between Renal Function and PK**

458

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

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

466
467 The intent of the modeling procedure is to provide a rational quantitative basis for dosage
468 recommendations in the drug's labeling. The model itself may be described in the clinical
469 pharmacology section of the labeling.

470
471 The reported modeling results should include estimates of the parameters of the chosen
472 model as well as measures of their precision (standard errors or confidence intervals).
473 Prediction error estimates are also desirable (e.g., confidence bounds for prediction of
474 clearance for the drug and its active metabolites over a range of CL_{CR} or eGFR).

C. Development of Dosing Recommendations

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

486
487 For some drugs, such as drugs eliminated primarily by metabolism or biliary secretion, even
488 severe renal impairment may not alter PK sufficiently to warrant dosage adjustment. A
489 sponsor could support this conclusion by providing an analysis of the study data to show that
490 the PK measurements most relevant to therapeutic outcome in patients with severe renal
491 impairment are similar to those in patients with normal renal function.

VI. LABELING

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

A. Highlights of Prescribing Information (Highlights)

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501 It may be appropriate to include in the Highlights a concise summary of information detailed in
502 other sections of the Full Prescribing Information (e.g., Dosage and Administration,
503

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

506

B. Dosage and Administration

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

511

- 512 • If there is a need for dosage adjustment in patients with renal impairment, it should
513 be noted and the adjustments described, either globally (reduce by 50% in patients
514 with moderate renal impairment (creatinine clearance of 30-59 mL/min as estimated
515 by Cockcroft-Gault or eGFR of 30-59 mL/min/1.73 m² as estimated by MDRD)) or
516 in detail, as the following table illustrates.

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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

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^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

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544 A subsection in the Use in Specific Populations section may be included (e.g., “Renal Impairment”)
545 to briefly describe clinically relevant information about patients with renal impairment. For
546 example, a concise summary of the clinical implications of differences in response or
547 recommendations for use of the drug in patients with renal impairment should be included in this
548 subsection, with a reference to the Dosage and Administration, Contraindications, Warnings and
549 Precautions, and Clinical Pharmacology sections, as appropriate, for more detailed information.
550

E. Overdosage

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553 Although the primary objective of a hemodialysis study is to evaluate the need for dosing
554 adjustments in ESRD, additional information regarding the value of hemodialysis in overdose
555 situations may reasonably be garnered from the results of such studies. In situations in which this
556 information is known, the Overdosage section could note the extent of elimination by hemodialysis
557 and whether hemodialysis is (or is not) known to be useful in treating an overdose.
558

F. Clinical Pharmacology

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561 In general, the more detailed study results from renal impairment studies should be presented
562 in the pharmacokinetics subsection of the Clinical Pharmacology section, with the clinical
563 implications described in Use in Specific Populations and, where appropriate, Dosage and
564 Administration, Contraindications, or Warnings and Precautions. The pharmacokinetics
565 subsection should include information on the following, when appropriate and applicable:
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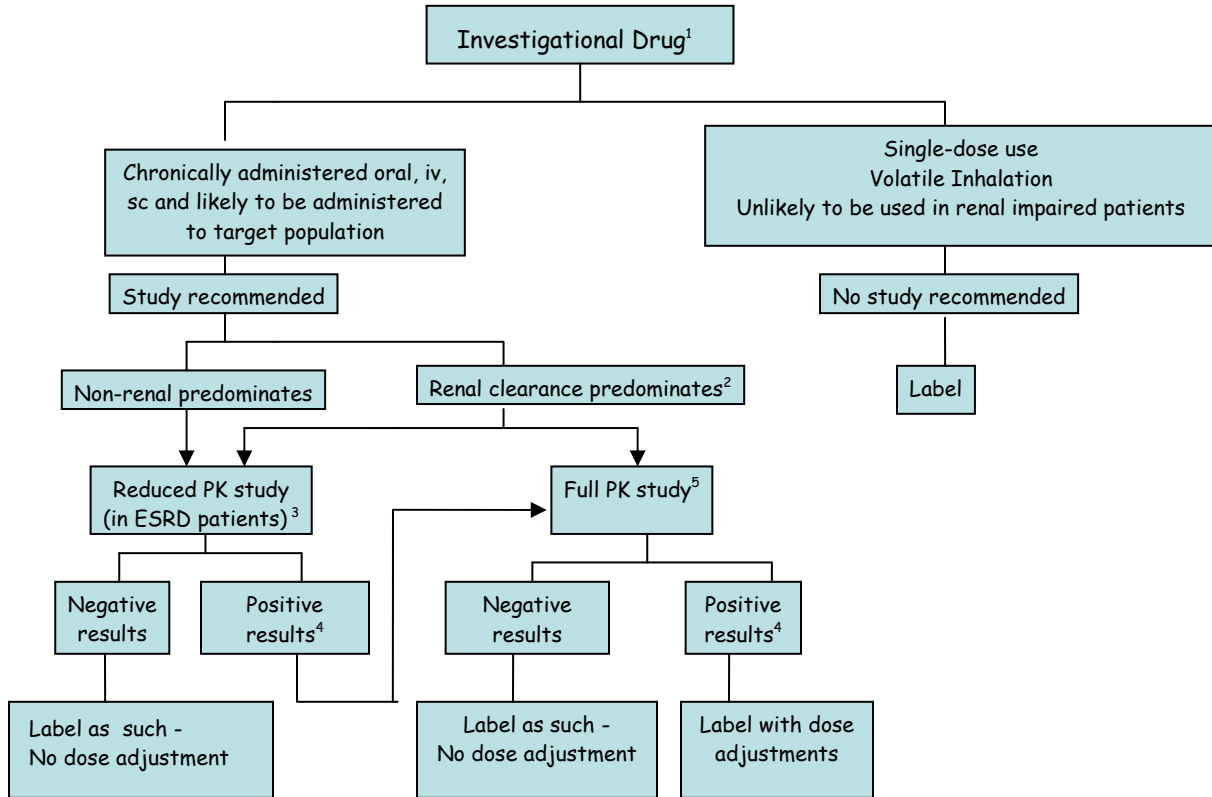
- 567 • Mechanism of renal elimination (e.g., filtration, active secretion, or re-absorption) and
568 transporters that may be involved
569
- 570 • Percentage of drug eliminated by renal excretion and whether it is eliminated unchanged
571 or as metabolites
572
- 573 • Results of studies comparing PK in normal subjects and subjects with varying degrees of renal
574 impairment (i.e., the studies described in IV.A and IV.B) and methods used to stratify the
575 subjects
576
- 577 • Disposition of metabolites in patients with impaired renal function (if applicable)
578
 - 579 • Effects of renal impairment on protein binding of parent drug and metabolites (if
580 applicable)
 - 581
 - 582 • Effects of changes in urinary pH or other special situations that should be mentioned
583 (e.g., tubular secretion inhibited by probenecid), if applicable
584
 - 585 • Effects of impaired renal function on stereospecific disposition of enantiomers of a
586 racemic drug product, if there is evidence of differential stereoisomeric activity or
587 toxicity, as applicable

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



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

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