Guidance Snapshot

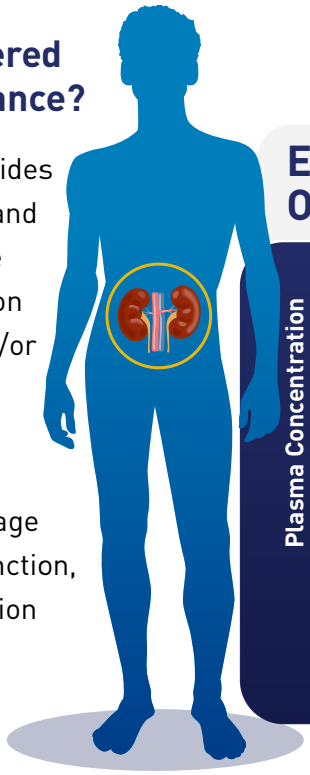
U.S. FOOD & DRUG ADMINISTRATION

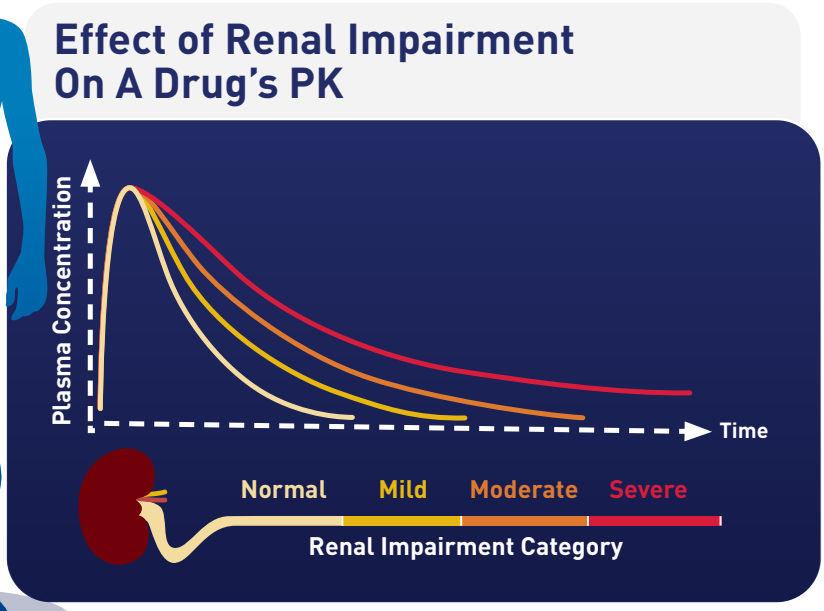
Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing

Final Guidance

What is Covered in This Guidance?

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

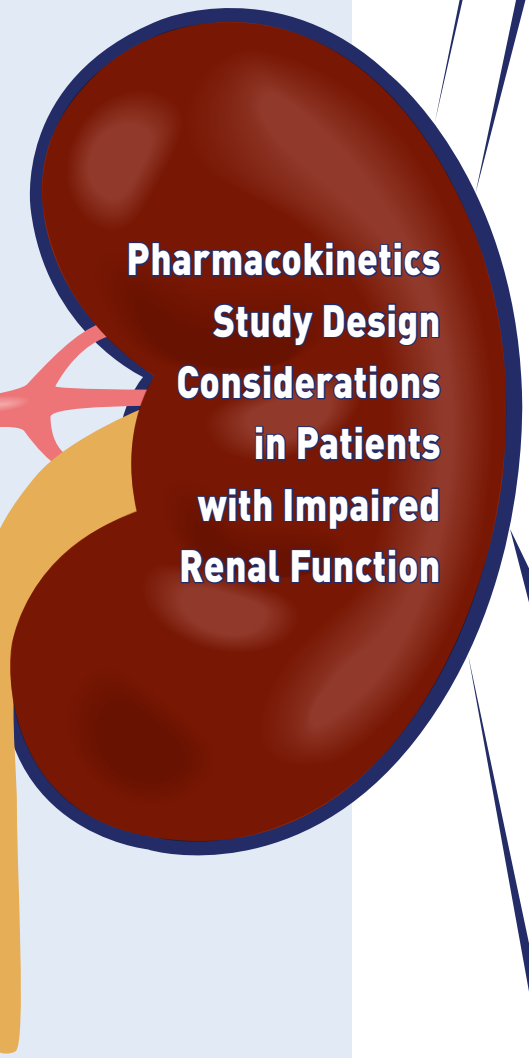




Why is This Guidance Important?

The kidneys are involved in the elimination of many drugs. As a result, it is important to characterize a drug's PK in subjects with impaired renal function to provide appropriate dosage recommendations. This guidance provides recommendations for the characterization of the effect of impaired renal function on a drug's PK. It also recommends that this characterization be done early in drug development, with the goal of enabling the enrollment of patients with impaired renal function in late-phase clinical trials by allowing appropriate prospective dosage adjustment. The guidance also recommends that the exclusion of patients with impaired renal function from clinical trials should be justified and discussed with the relevant review division.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document.
To learn more about PK in patients with impaired renal function, read the guidance.
To see additional Guidance Snapshots, check out the pilot program.



Scenarios that warrant a renal impairment study

- When renal function likely alters the PK of a drug or metabolites
- For therapeutic proteins and peptides <69 kDa
- For drugs likely to be used in patients receiving dialysis or continuous renal replacement therapy (CRRT) dialysis

Study design considerations

- For a full study design:
  - Study participants should range from normal to severe renal impairment and kidney failure, not receiving dialysis
  - A single-dose study is usually sufficient
- For a reduced study design, enroll patients with severe renal impairment or kidney failure, not receiving dialysis
- The impact of intermittent dialysis on a drug's PK should be evaluated both while the patient is on dialysis and off dialysis
- Similar principles to that of intermittent dialysis can be considered, while taking into account unique aspects of CRRT to ensure generalizability of dosage recommendations.
- Because of widespread availability and use in clinical practice, the estimated glomerular filtration rate (eGFR) is recommended
- When providing a recommended dosage in adult patients with renal impairment use eGFR in mL/minute rather than eGFR in mL/minute/1.73 m^2

Alternative strategies

- Alternate design approaches may be appropriate to facilitate enrollment of patients with renal impairment in Phase 3 clinical trials
- Early characterization of data, e.g., from Phase 1 or Phase 2 studies, along with modeling and simulation can be used to facilitate enrollment in Phase 3 trials
- Assessment of PK changes in renal impairment in phase 2/3 trials may be appropriate if there is sufficient enrollment

Data Analysis

- Plasma concentration and urinary excretion data, where available, should be analyzed to estimate PK parameters of a drug and active metabolites
- The relationship between renal function and PK should be assessed both using categorical analysis (by renal function groups) and using renal function as a continuous measure
- The effect of renal impairment on the exposure-response relationships should be understood for accurate dosing

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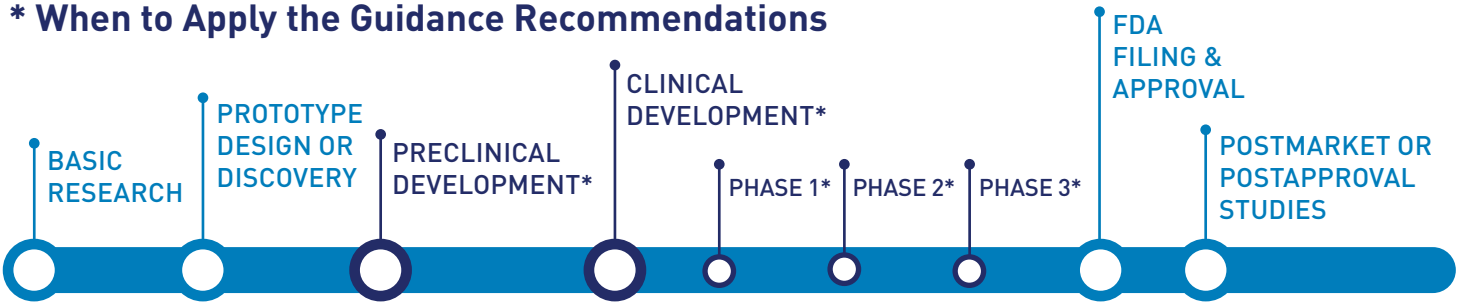
Background and Updates

This version replaces the draft guidance entitled, Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing (September 2020), and provides updated recommendations on the following topics:

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

Drug Development Timeline

*** When to Apply the Guidance Recommendations**



Starting in Preclinical Development and Through Clinical Development:

Drug development programs should include an early characterization of the effect of impaired renal function on a drug's PK, with the goal of enabling the enrollment of this population in late-phase trials by allowing appropriate prospective dosage adjustment. Early characterization can be based on data obtained from phase 1 or phase 2 studies. Alternatively, this information can be obtained by using modeling and simulation strategies, for example, physiologically based pharmacokinetic modeling and simulation. Such approaches allow sponsors to obtain clinical experience using the proposed dosing regimen in patients with impaired renal function and thus better ensure that the trial findings will be applicable to the population likely to use the drug, should the drug be approved.

Guidance Recap Podcast

Hear highlights from FDA staff

Speaker(s): Martina Sahre, PhD, Policy Lead in the Center for Drug Evaluation and Research's Office of Clinical Pharmacology

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