FDA Briefing Document

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

May 7, 2019

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The committee will discuss the following topics: (1) approaches to evaluate the effect of renal impairment on drug exposure, and (2) best practice considerations for translating pharmacokinetic (PK) information into dose individualization instructions. The background package is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Office Director Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Clinical Pharmacology
M E M O R A N D U M

Date:	*April 10, 2019*
From:	*Issam Zineh, PharmD* *Director, Office of Clinical Pharmacology* *Office of Translational Sciences, CDER, FDA*
To:	*Chair, Members and Invited Guests* *Pharmaceutical Sciences and Clinical Pharmacology* *Advisory Committee (PSCP)*
Subject:	*Overview of the May 7, 2019 PSCP meeting*

We are convening this meeting to discuss topics related to the evaluation of subjects with renal impairment during drug development, including their participation in phase 2 and phase 3 efficacy and safety trials. The ultimate goal of this evaluation is to determine dosing regimens for inclusion in product labeling for patients with the full range of renal function. A summary of the topics and the questions for the committee are included below.

Draft Topics for Discussion

Topic 1: Evaluation of the effect of renal impairment on drug exposure

Many registration trials exclude patients with advanced kidney disease. The dosing instructions included in prescription drug labeling for these patients are commonly derived based on our understanding of the change in the investigational drug's pharmacokinetics (PK) in subjects with varying degrees of renal function. The necessary information can be collected in several ways.

The most common current approach to determine dosing instructions for patients with varying degrees of renal function begins with a stand-alone "full design" or "reduced design" renal impairment study. Most often, a full design study (which compares

subjects with mild, moderate, and severe renal impairment with subjects with normal renal function) is conducted for drugs with significant renal elimination, and a reduced design study (evaluation of subjects with severe renal impairment against those with normal renal function) is conducted for drugs that do not have significant renal elimination. In addition to conducting stand-alone renal impairment studies, drug development programs often use the findings from population PK (popPK) analysis. PopPK analysis leverages the PK information across all the studies available in a drug development program for which PK samples have been obtained. However, late-stage clinical trials often include limited numbers of patients with renal impairment, so stand-alone renal impairment studies provide most of the information regarding the need for dose adjustment. This current typical paradigm is a retrospective approach to dose individualization that excludes an important patient population from the assessment of efficacy and safety.

We would like to explore alternative paradigms that encourage inclusion of patients with renal impairment in later-stage clinical trials. Such paradigms could predict the impact of renal impairment on the pharmacokinetics of the drug based on available data and modeling, without a stand-alone, full-design renal impairment study. If deemed necessary, doses may be adjusted for patients with impaired renal function. Inclusion of these patients in clinical trials would lead to more generalizable efficacy and safety assessments. Because many late-stage clinical trials include sparse PK sampling for popPK analysis, characterization of the effect of renal impairment on pharmacokinetics would be possible. If patients with severe renal impairment and those with end-stage renal disease on dialysis must be excluded from late-phase trials for safety reasons, a reduced design study and a dialysis study (where applicable) would be the only stand-alone characterization needed for the drug development program.

- *What alternative drug development paradigm(s) would encourage the inclusion of patients with all (or most) degrees of renal impairment in late-stage clinical trials, without the need for a stand-alone renal impairment study? Discuss the advantages and disadvantages of these paradigms as compared to the current paradigm.*

Topic 2: Translation

For the subgroup of patients with kidney disease, especially those with severely impaired renal function (often excluded from late stage clinical trials), PK data or predictions may be the main source of information for dose individualization. Dose individualization is achieved by invoking the concept of ‘exposure-matching’ to subjects with normal renal function under the assumption that the ‘exposure-matching’ will result in a benefit-risk similar to that observed in the registration trials.

During drug development, evaluations of the effect of renal disease tend to focus mostly on the effect on drug clearance and the resulting changes in drug exposure. However, renal disease can affect other organs, alter physiology, and patients with renal disease can present

with comorbidities. Both renal disease and the presence of comorbidities could theoretically predispose patients to an increased incidence of adverse events, altered pharmacodynamics, or altered efficacy, thereby altering the exposure-response relationship and/or overall benefit/risk. To date, there is limited information in the literature about the impact of renal disease on drug response. Current practices in drug development often do not allow the assessment of differences in the exposure-response relationship, because patients with advanced kidney disease are either not enrolled or not enrolled in sufficient numbers.

- *Is it reasonable to assume that a drug's exposure-response relationship will usually not be significantly different between patients with impaired renal function and patients included in the registration trials? Please discuss the situations where the assumption of similar a exposure-response relationship may not apply. Often for exposure matching purposes, the normal renal function group serves as the reference group. However, we propose the reference group should be selected based on the understanding of benefit/risk for the drug. Generally, the reference group should be one with an acceptable benefit/risk-relationship and be more proximal in terms of renal impairment to the group in question (E.g., severe vs. moderate instead of always severe vs normal).*

- *There are multiple approaches for establishing an "exposure match" (i.e., matching based on point estimate, confidence interval-based approaches, exposure matching 5th and 95th percentile, etc.). Please discuss the criteria for choosing one approach over another.*

Background

In the United States, an estimated 14.8% of the adult population have chronic kidney disease (CKD), and those with CKD Stages 3 - 5 account for approximately half of that population (*1*). The prevalence of CKD increases with age, and patients with later-stage CKD often receive multiple mediations, for example lipid-lowering agents, cardiovascular medicines, anti-depressants, and anti-infective agents, creating a challenging polypharmacy situation (*2*). Frequently however, patients with advanced kidney disease are explicitly excluded from participation in late-phase clinical trials, precluding an assessment of the effects of severely impaired kidney function on the patient's clinical response. This exclusion leads to a lack of information on drug dosing for patients with later-stage CKD.

Generally, the effect of impairment in renal function on the pharmacokinetics of drugs is well understood. After entering the body, drugs are eliminated by a variety of mechanisms. If a drug is eliminated primarily through renal excretion, impaired renal function often alters the drug's pharmacokinetics to an extent that the dosage regimen may need to be changed from that used in patients with normal renal function. The most obvious type of change in the pharmacokinetics of a drug arising from impaired renal function is a decrease in renal excretion of a drug or its metabolites. However, other changes, for example, absorption, plasma protein binding, and/or tissue distribution of a drug can also occur.

Literature reports indicate that impaired renal function can alter some drug metabolism and transport pathways in the liver and gut (*3, 4*). These changes may be particularly prominent in patients with severely impaired renal function. However, the degree of impairment in renal function at which these changes are observed and the underlying mechanisms causing impairment are not fully understood. 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 pharmacokinetics in subjects with impaired renal function to provide appropriate dosing recommendations.

Current Typical Paradigm for Determining Dosing Instruction in Patients with Impaired Renal Function

The typical current approach to determine dosing instructions for patients with varying degrees of renal function begins with a stand-alone renal impairment study, either full design or reduced design. Often, a full-design study is conducted for drugs with significant renal elimination, and a reduced design study is conducted for drugs that do not have significant renal elimination. Full design, here, refers to inclusion of study participants spanning the entire range of CKD, i.e. from mild to severe renal impairment or even kidney failure. Reduced design refers to the inclusion of only the severe renal impairment group, to assess a "worst-case" scenario. In addition to conducting stand-alone renal impairment studies, drug development programs often use the findings from

popPK analysis. PopPK analysis leverages the PK information across all the studies available in a drug development program and often includes information from phase 2 and phase 3 efficacy and safety trials. The current draft guidance provides recommendations and guidance to assist sponsors in planning studies to assess the influence of renal impairment on a drug's pharmacokinetics and translating the information to inform dosing and labeling.(*5*)

Full pharmacokinetic study design

For drugs that are predominantly cleared by the kidneys, i.e. the systemically available fraction that is excreted unchanged in urine is greater than 30%, a full PK study design is typically used. This study should have adequate representation of subjects with varying degrees of renal function to characterize the continuous relationship between renal function and drug clearance. If the study is conducted early in drug development, this information can allow for the inclusion of patients with impaired renal function in late-stage trials as well as inform dosing recommendations in the labeling.

The categories of renal function described in Table 1 can also be useful for deriving dosing recommendations.

Table 1. Classifications of Renal Function[a, b, c] 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[d]	<15 or dialysis patients on non-dialysis days

[a]In some situations, collection of 24-hour urine samples to measure creatinine clearance, or the clearance of an exogenous filtration marker, can provide better estimates of renal function than serum creatinine-based prediction equations.

[b] eGFR(glomerular filtration rate): 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 m^2.

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

[d] 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.

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 pharmacokinetics. If the typical patient population is composed of older subjects and includes women, the control group should not consist of only healthy young male volunteers with normal renal function. Because kidney function declines with age, it may be appropriate for the control group for a drug intended for use only in older individuals to consist of patients with normal renal function and mild renal impairment (e.g., GFR ≥60 mL/min). In other cases where use of the drug is anticipated in younger patients with normal kidney function, the control group should include subjects with normal renal function (i.e., GFR ≥90 mL/min) to characterize the impact of impaired renal function on the PK of the drug across the spectrum of renal function.

The number of subjects enrolled in each renal function group should be sufficient to ensure precise estimation of the relevant PK parameters. A single-dose study is considered sufficient to accurately describe the pharmacokinetics for the drug and potentially active metabolites, especially when the drug and active metabolites exhibit dose-proportional and time-independent pharmacokinetics at the concentrations anticipated in the patients to be studied. Plasma or whole blood as well as urine samples should be collected and analyzed for the parent drug and any metabolites of interest. The

frequency and duration of plasma sampling and urine collection should be sufficient to accurately estimate the relevant PK parameters for the parent drug and its active metabolites.

Reduced pharmacokinetic study design

For drugs that are predominantly eliminated via nonrenal routes and are 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 that elicits the highest impact of renal impairment on the PK of the drug. Prior submissions to the Agency and literature reports suggest that for such a study, subjects with severe impairment in renal function (see Table 1) may be considered to represent the worst-case scenario (*6*). If a reduced design PK study shows a clinically relevant effect on the PK of the drug in patients with severely impaired renal function, the sponsor should characterize the effect on the drug's pharmacokinetics in patients with the remaining intermediate levels of impaired renal function (see Table 1). If no difference in a drug's pharmacokinetics is observed between patients at the extremes of renal function, then no further study is necessary.

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 impairment, popPK analyses of data from phase 2 or phase 3 clinical trials may be sufficient to characterize the impact of renal function on drug exposure and to understand the consequences of these changes on the effectiveness and safety of the drug.

In phase 2 or phase 3 studies used for popPK analyses, patients are typically sparsely sampled to obtain plasma drug concentration data. A popPK study design and the resulting analysis should retain some of the critical components mentioned in the previous section on full study designs. Important considerations include sufficient numbers of patients over a range of renal functions, accurate records of dosing and sample collection times, and adequate numbers of samples per patient.

Data analysis and determining dosing recommendations

The primary intent of such data analysis is to estimate the impact of renal function on drug clearance and to use such information to derive appropriate dosing recommendations.

Plasma concentration data and urinary excretion data should be analyzed to estimate various parameters describing the PK of the drug and its active metabolites. The PK 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 PK 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.

The objective is to construct mathematical models that adequately describe the relationship between the estimated renal function and relevant PK parameters to inform dosage recommendations in the drug labeling. Generally, a regression approach is recommended to estimate renal function, and the PK parameters are treated as continuous variables. This method is preferred, compared to an analysis in which estimated renal function is treated as a categorical variable corresponding to the normal, mild, moderate, and severe impaired renal function groups. In either case, the potential for confounding due to differences in baseline covariates that may affect a drug's pharmacokinetics (e.g., age, gender, race, and weight) should be evaluated.

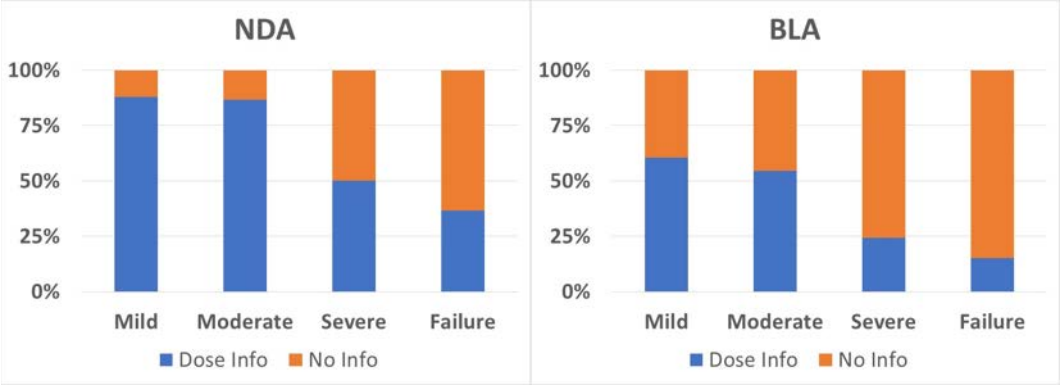
Specific dosing recommendations are generally developed based on the results of the stand-alone study that characterizes the relationships between creatinine clearance or eGFR and relevant PK parameters. Typically, the dose, dosing interval, or both are adjusted to produce a range of plasma concentrations of drug or active metabolites that is similar in subjects with normal renal function and subjects with impaired renal function.

Limitation of the current paradigm

Typically, the late-phase clinical trials in new drug development include a well-defined patient population to minimize variability and increase the ability to characterize the magnitude of the effect of the drug. Thus, trials often exclude participation of certain patients with comorbidities or concomitant treatments or factors that could mask the effect of intervention. Such exclusions limit the generalizability of clinical trial results and can result in an evidence gap for certain patient subgroups that will eventually receive the drug upon approval.(*7*) Patients with advanced kidney disease are often excluded from late stage clinical trials. For example, in a non-random sample of 38 individual drug trials submitted to FDA, 60% applied exclusions based on kidney function calculated by a commonly used estimating equation. Most of the trials used a cutoff value of 60 mL/min.(*8*) Stand-alone clinical pharmacology studies in subjects with impaired renal function often bridge the gap and provide instructions for use. However, this approach relies on the fundamental assumption that the exposure-response relationships are similar between the subgroup of patients with impaired renal function and those that were studied in the clinical trials. Further, there is an underlying concern that patients with kidney disease, even after dose adjustment, may have effectiveness or safety profiles different from patients without that condition.(*8-10*) Dosing information in the labeling is often provided only for mild and moderate renal impairment groups, but not for patients with severe impairment or kidney failure (Figure 1). Of note, when renal impairment is not expected to affect a drug's pharmacokinetics, for example, if the drug is a biologic, there is often popPK analysis for the range of patients studied in clinical outcome studies. This information sometimes translates to labeling language indicating that no dose adjustment is needed in mild or moderate disease, while stating that the

impact of severe renal impairment, on safety, efficacy, or the drug's pharmacokinetics is unknown.

Figure 1. Dosing by renal function category in the approved labels for new drug applications (NDA; N = 82) and biologic license applications (BLA; N = 33). The internal survey was conducted for products approved from 2016 to 2018.



Further, the labeling for patients with severe impairment in renal function often resorts to statements like, *"Dosing recommendations cannot be provided,"* or *"Patients with severe renal impairment were not included in Phase 3 studies, and the impact on pharmacokinetics in that population is unknown."* Hence, there is a need for an alternative paradigm that will address these evidentiary and labeling gaps.

Proposed Alternative Paradigm

From a drug development perspective, the stand-alone renal impairment studies that are conducted to characterize the impact of impairment in renal function on the pharmacokinetics of a drug are often conducted late in the development cycle. This lack of data limits the ability to include these patient subgroups in the phase 3 trials. However, a well-planned drug development program could enable the inclusion of such patients in late-phase trials. The early availability of critical information on drug metabolism, disposition, and elimination has significantly improved. Based on the information in the early-phase studies, and with increasing confidence in modeling and simulation modalities, it is possible to consider alternative paradigms to increase enrollment of patients with more severe degrees of renal impairment into clinical studies. Thus, sponsors could predict the impact of renal impairment on the pharmacokinetics of the drug, either based on the understanding of the pharmacokinetics of a new molecular entity or using modeling, without a stand-alone, full-design renal impairment study. Patients with impaired renal function could then be included in later-stage clinical trials (e.g., dose selection, registration trials), with or without prospective dose adjustment based on the predictions. Such an approach would allow collection of the necessary clinical experience to inform use in patients with renal impairment. Given that sparse PK sampling is often employed in late stage clinical trials, the effect of renal impairment on the pharmacokinetics of a drug can also be characterized.

Given the above considerations, in situations where patients with severe renal impairment and end-stage renal disease are excluded from late-phase trials for safety reasons, a reduced-design study and a dialysis study (where applicable) would then be the only stand-alone characterization needed for the drug development programs.

Our experience with such alternative paradigms is limited and presents its own challenges. For registration trials, which include prospective dosing, post hoc analyses of certain subsets may reveal that the prospective dose adjustment either:

1. Achieved the intended benefit/risk balance
   OR
2. Did not achieve the intended benefit/risk balance
   a. Diminished efficacy
      OR
   b. Prospective dose adjustment did not reduce adverse events such that the benefit/risk was lower compared to overall population.

However, the interpretation of the results of these analyses can be challenging. There is a clear need for developing best practices for inclusion of patients with impaired renal function in late stage clinical trials and analysis of the data to inform use.

Translation

Irrespective of the paradigm, specific dosing recommendations are typically constructed based on the overall understanding of the relationship between renal function, drug exposure, and the exposure-efficacy/safety relationship. For drugs with a wide therapeutic range, changes in the drug's pharmacokinetics based on renal function may not always result in a dosage adjustment for patients with renal impairment. When there is a need for dosage adjustment in patients with impaired renal function, it is typically based on exposure-matching to a reference group with an acceptable benefit-risk profile for the drug. Though it seems simple, the concept of exposure-matching is nuanced and is relevant for situations beyond just deriving dosing in patients with kidney disease.

First, the fundamental underlying assumption of exposure-matching is that the exposure-response relationships for efficacy and safety are similar in the subgroup for which the dosing is being derived and the population that is being relied upon as reference exposure group. In general, given the lack of information, it is not possible to evaluate this assumption. However, there have been a few instances where such information was available.

Next is the choice of the reference group. Conventionally, the reference group of interest is the subgroup with normal/preserved renal function. However, late-phase clinical trials may include patients with some degree of impairment in renal function. Often this includes patients with mild impairment and to some extent patients with moderate renal impairment, with or without a dose adjustment. In such situations, it is not clear whether

the reference group for exposure matching should always be patients with normal renal function or if the choice of the reference group should be informed by the range of acceptable clinical experience. For example, exposure-matching to subgroup of patients that are most proximal in renal function and with an acceptable benefit-risk profile could be considered as an alternative.

Lastly, there are multiple approaches to exposure-matching. Some of the commonly applied approaches are:

1. **Matching to a point estimate**: The exposure matching is based on deriving doses for renal impairment subgroups based on the Geometric Mean Ratio (GMR) in the area under the concentration time curve (AUC). This approach is usually applied to the results of stand-alone renal impairment studies. For example, if the GMR for renal impairment subgroup relative to normal is 2, the dose in the renal impairment group is reduced by half relative to the dose for individuals with normal renal function.

2. **Matching the confidence interval of GMR to predefined 'no-effect boundary'**: In this approach, the 'no-effect boundary' is determined based on the understanding of the dose-exposure-response relationships. In the absence of reliable exposure-response information, a totality of evidence or a conservative standard of bioequivalence principle (0.8 – 1.25) is invoked to determine the 'no-effect boundary.' Exposure matching is based on ensuring the 90% confidence interval of the expected AUC with dose adjustment falls within the 'no-effect boundary'[Clinical DDI Guidance (*11*)].

3. **Matching to the range of exposures observed for the reference group**: In this approach, the range of exposures observed in the registration trials is considered to have an acceptable benefit/risk profile. Dose adjustment in the renal impairment subgroups is derived based on ensuring that the predicted exposures fall within this range. For example, dosing in patients with renal impairment that result in exposures that fall within 5th and 95th percentile of those observed in the reference group in clinical trials [suggested as an example in the Pediatric Clinical Pharmacology guidance (*12*)].

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