Estimating Renal Function in Drug Development: Time to Take the Fork in the Road

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ABSTRACT (240 words, max 250 words)

Renal function is the most commonly applied patient-specific, quantitative variable used to determine drug doses. Measurement of renal function is not practical in most clinical settings; therefore, clinicians often rely on estimates when making dosing decisions. Similarly, renal function estimates are used to assign subjects in Phase 1 pharmacokinetic studies, which inform dosing in late phase clinical trials and ultimately the product label. The Cockcroft-Gault estimate of creatinine clearance has been the standard renal function metric; however, this paradigm is shifting towards the Modification of Diet in Renal Diseases (MDRD) estimate of glomerular filtration rate (GFR). The proportion of approved new drug labels with dosing recommendations based on the MDRD equation was 16.7% in 2015, 70.0% in 2016, and 46.7% in 2017. Disharmonious recommendations from the United States Food and Drug Administration and the European Medicines Agency will continue to increase this heterogeneity in the assessment of renal function in drug development and negatively impact industry, health systems, and clinicians. In this review, we discuss the current regulatory guidance for the conduct of renal impairment pharmacokinetic studies and review the implications of this guidance across the medication use system with three recently approved antibiotics: ceftazidime/avibactam, delafloxacin, and meropenem/vaborbactam. Finally, we suggest measuring GFR in Phase 1 studies and employing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to integrate data across clinical trials. This will help to harmonize CKD staging, population pharmacokinetic analyses, and dosing by estimated renal function.

Keywords: regulatory science, CKD-EPI, Cockcroft-Gault, creatinine clearance, drug development, glomerular filtration rate, MDRD

INTRODUCTION

Precision pharmacotherapy relies on an understanding of the factors contributing to variability in drug exposure (pharmacokinetics [PK]) or drug effect (pharmacodynamics [PD]) within patient populations.[1] While precision medicine is frequently associated with use of

clinical pharmacogenomics to select the right drug, dose adjustments based on genotype have been only minimally implemented into the regulatory process and clinical practice.[2] Because of the paucity of genomic information currently available to clinicians, dose individualization relies on measureable factors impacting drug PK, namely, patient body size and eliminating organ function.[1] The kidneys are responsible for the elimination of many classes of xenobiotic compounds and their metabolites, making renal function the most common factor used to individualize drug dosing. However, methods used to measure renal function through the glomerular filtration rate (GFR), or surrogates thereof, are time intensive and impractical in most clinical settings.[3] Thus, drug dosing is largely determined using estimates of GFR obtained from equations based on demographic variables and one or more renal biomarkers.[3]

The Cockcroft-Gault (C-G) estimate of creatinine clearance (eCrCL) has been the standard used to enroll patients with renal impairment into Phase 1 PK studies, inform dosing protocols in late phase clinical trials, and stratify dosing schedules in product labeling.[4] However, since publication of draft guidance from the United States Food and Drug Administration (FDA) in 2010, this paradigm has been shifting towards the Modification of Diet in Renal Disease (MDRD) estimate of glomerular filtration rate (eGFR), despite the lack of a clear recommendation in favor of this equation over the C-G.[5, 6] Conversely, the European Medicines Agency (EMA) recommends an exogenous measure of GFR be used in these early phase clinical trials.[7] The lack of harmony between these regulatory agencies has created an environment of uncertainty and heterogeneity in the development of drugs impacted by renal function. This variability in the assessment of renal function has important implications for industry, regulators, health systems, and clinicians. Furthermore, the current trajectory towards increasing use of the MDRD equation in these settings may not be

optimal. In this review, we highlight the current regulatory guidance with respect to assessment of renal function, discuss the implications for all members of the medication use system, and suggest a way forward using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) to harmonize drug dosing across the entire distribution of renal function.

RENAL FUNCTION ESTIMATION IN DRUG DEVELOPMENT

The FDA recommends renal impairment PK studies for many types of investigational compounds, not just those primarily eliminated unchanged in urine or those affected by the dialysis process.[5] There is increasing recognition that hepatic and biliary drug metabolizing enzymes and transporters are altered in chronic kidney disease (CKD).[8] Because of this, the FDA recommends reduced or full renal impairment studies for compounds primarily metabolized or secreted in bile as well as therapeutic proteins with molecular weights under 69 kDa. Thus, most investigational drugs intended for chronic administration will be studied to some degree in subjects with renal impairment.[5]

The FDA suggests that subjects should be enrolled into Phase 1 renal impairment studies based on estimated GFR given the impracticality of measuring GFR in most clinical settings. This guidance recognizes the C-G equation as the historical standard for drug dosing in renal impairment but acknowledges that use of the MDRD is increasing in clinical practice. The stated position of the FDA is that “either the C-G or MDRD equation can be used to assign subjects to a renal impairment group or stage” but “PK results should be shown for both C-G estimates of creatinine clearance and eGFR”.[5] Measured CrCL obtained via timed urine collections can be considered in individuals with abnormal variation in diet

(vegetarian, creatine supplements) or altered muscle mass (amputation, malnutrition, muscle wasting) but is not recommended routinely due to methodological challenges and high intra- and inter-day variability. While not included in the main text of the guidance, a table footnote states that measured GFR or CrCL may also be superior to prediction equations for subjects with acute renal failure, extremes of age or body size, and those undergoing kidney replacement therapy.

In contrast to the FDA, the EMA recommends measuring GFR using an exogenous compound due to improved accuracy over equation-based estimates.[7] Furthermore, the EMA recommends reporting all GFR values, whether measured or estimated, in absolute units (mL/min) rather than normalized to subject BSA. The rationale for this difference is that renal clearance of drugs in individuals is proportional to absolute GFR rather than the BSA-normalized values used to diagnose and stage CKD. The EMA states that presentation of data from Phase 1 renal PK studies should be made using an estimate of GFR, based on serum creatinine (Scr) or cystatin C, or an estimate of creatinine clearance. The MDRD, C-G, and CKD-EPI equations are all listed as appropriate estimates; however, no preference is given to one equation over another by the EMA.[7]

The recommendations from the FDA and EMA discussed above apply only to the design and conduct of renal impairment PK studies in adult subjects. For pediatric subjects, the FDA recommends using measured CrCL or GFR determined via an exogenous indicator for enrollment with extrapolation to larger efficacy or population PK studies using the modified Schwartz equations incorporating standardized Scr and/or cystatin C.[5, 9] Unlike the FDA, the EMA indicates that results demonstrating altered PK based on changes in GFR in adult patients can be extrapolated to pediatric patients in most cases.[7]

IMPLICATIONS ACROSS THE MEDICATION USE SYSTEM

The lack of a single standard for the assessment of renal function in Phase 1 studies impacts all stages of the medication use system from pharmaceutical companies to clinicians taking care of individual patients. In this section, we discuss how the absence of a standardized method for quantifying renal function in early phase clinical trials leads to heterogeneity in study design, modeling of pooled data, regulatory review, electronic reporting of renal function, and ultimately drug dosing by individual clinicians. This heterogeneity will be highlighted throughout this section using the example of the three systemically available antibiotics approved by the FDA between 2015 and 2017: ceftazidime/avibactam (CZA), delafloxacin (DLX), and meropenem/vaborbactam (M/V).[10-12]

Industry. When designing dedicated renal impairment studies, sponsors of investigational therapeutics must choose a method to enroll subjects into groups based on kidney function. The choice between the C-G and MDRD equations, as recommended in the 2010 FDA guidance, is non-trivial and may significantly impact the assignment of individual subjects to renal groups. The discrepancy in units between the MDRD and C-G equations, as well as the inherent biases of each equation, can translate to discrepancies in subject assignment across renal strata.

The FDA recommends reporting the results of the MDRD equation normalized to BSA (mL/min/1.73 m^2) rather than in absolute units (mL/min), which results in under-prediction of true absolute GFR in subjects with larger than average body size. Furthermore, the C-G equation intrinsically overestimates measured absolute GFR by approximately 15%

on average with even greater error in subjects with large body size.[13-17] The combination of these biases leads to significant discordance between the two methods when assigning subjects to renal function groups. A review of pooled Phase 1 data from 36 new molecular entities approved by the FDA between 1998 and 2010 found 35.8% discordance (kappa = 0.54, weight-kappa = 0.73) between the C-G and BSA-normalized MDRD equations.[18] Notably, this discordance decreased to 22.2% when using the MDRD equation expressed in absolute units (kappa = 0.71, weighted-kappa 0.87).

Table 1 depicts a "real-world" example of this discordance using Phase 1 data included in the FDA review of DLX, a fluoroquinolone antibiotic approved in 2017.[11, 19] Subjects were enrolled into four equally sized groups (n = 8) by eGFR; however, assignment of subjects by eCrCL demonstrated significant changes in group size and composition. Six subjects classified as having renal impairment by eGFR were classified as controls by eCrCL and only 3 of 8 subjects in the severe renal impairment category remained when classifying by eCrCL. These data demonstrate the inadequacy of the current approach of presenting PK data stratified by both eCrCL and eGFR as a method to deal with the discordance between these measures.

Clearly, the choice of GFR estimate can have a significant bearing on enrollment of subjects into the reference group in Phase 1 renal impairment studies. This is particularly relevant as the relative drug exposure between control subjects and those with renal impairment ultimately informs dose adjustments used in Phase 3 clinical trials. The MDRD study equation was developed using data from subjects screened for enrollment in a trial targeting participants with CKD (GFR ≤ 55 mL/min/1.73 m^2). [6, 13] Due to the enrollment criteria for the original study, measured GFR values in or near the normal range were under-represented in dataset used to develop the study equation, which results in a

systematic bias towards underestimation of measured GFR in the setting of normal or near-normal kidney function (eGFR > 60 mL/min/1.73 m^2). This bias persists even after correction for isotope dilution mass spectrometry (IDMS) traceable serum creatinine values.[6, 14] Correspondingly, the National Kidney Disease Education Program (NKDEP) recommends to avoid reporting actual eGFR values above 60 mL/min/1.73 m^2 determined using the MDRD equation underscoring the limitations this equation to enroll subjects with normal renal function into Phase 1 studies.[20]

Figure 1 highlights the different strategies used to enroll subjects across the clinical programs of CZA, DLX, and M/V. Subjects were enrolled into the dedicated renal impairment PK studies using the C-G equation for CZA, the MDRD equation for DLX, and a hybrid approach for M/V.[19, 21, 22] The hybrid approach used in the Phase 1 study of M/V enrolled subjects into the healthy control group using the C-G equation (eCrCL > 90 mL/min) and the renal impairment groups via the MDRD equation (eGFR < 90 mL/min/1.73 m^2) to account for the limitations of the MDRD equation at near-normal values of eGFR.[22] Interestingly, despite the fact that the dedicated renal PK studies of both DLX and M/V used the MDRD equation to define renal impairment, exclusions and dose adjustments for renal dysfunction in their Phase 2 and 3 trials were based on eCrCL rather than eGFR (Figure 1).[23-26]

Pharmacometricians. Given the relatively small number of subjects with renal impairment enrolled across all phases of clinical drug development, analysis of pooled data is necessary to evaluate the effect of renal impairment on drug exposure across the population. Pharmacometricians use population modeling and simulation to perform structured

evaluation of covariate effects on drug PK. The resulting models are subsequently used for simulations to identify optimal dosing regimens designed to maximize the drug PD profile.

Defining an accurate covariate structure in the population PK model is reliant on the distribution of each covariate in the underlying population. Therefore, a measure or estimate of renal function which is valid and unbiased across the entire distribution of GFR is necessary to accurately assess the impact of renal function on drug PK using a population approach. The traditional renal dosing paradigm has been unidirectional and focused exclusively on renal impairment. It is increasingly recognized that a bidirectional strategy, employing adjustments for both renal impairment and augmentation, may be necessary. This is exemplified by the direct acting oral anticoagulant edoxaban, which carries a black box warning for reduced efficacy in patients with eCrCL > 95 mL/min, possibly due to under dosing in patients with good renal function.[27]

Glomerular filtration rate measured directly using an exogenous substance provides the most unbiased and accurate measure of renal function across the entire distribution; however, it is methodologically cumbersome and costly to implement in late phase clinical trials. Therefore, even if exogenously measured GFR becomes the standard for Phase 1 studies, as suggested by the EMA, it is unlikely to ever be useful for modeling of pooled data from all phases of clinical development. The C-G equation is valid across the entire distribution of renal function; however, it suffers from significant bias. The MDRD equation provides a more accurate and unbiased measure of GFR in renal impairment but systematically under-estimates GFR in subjects with normal or near-normal renal function.

Multiple challenges exist for pharmacometricians in modeling the PK of drugs eliminated by the kidneys. The use of renal function estimates that suffer from systematic

biases (e.g. >60 mL/min/1.73m^2 for MDRD) limits the utility of estimated renal function as a covariate in population PK model development. This limitation is also compounded by the inability of current serum creatinine-based estimates to account for intra-patient variability in PK due to the time-varying, dynamic nature of GFR and disease pathophysiology. Renal function estimates based on single serum creatinine measurements require those values to be obtained at steady-state. The estimation of GFR in clinical conditions such as sepsis and acute kidney injury is at present unreliable. This limitation of the common serum creatinine based renal function estimates impacts dose selection of drugs used to treat acute illnesses, such as the broad-spectrum antibiotics discussed here. Select drugs that are eliminated unchanged in urine can also cause acute kidney injury which adds an additional layer of complexity to population PK model development due to a potential reduction in clearance over time due to nephrotoxicity. Modeling and simulation of drugs to define dosing can also be impacted by the excipients used to solubilize them. For example, the intravenous formulation of DLX contains the excipient, sulfobutyl-ether-β-cyclodextrin (SBECD), which is primarily eliminated unchanged in urine.[11, 28] Studies in animal models suggest the risk for liver and renal injury increases when high concentrations of SBECD are present.[28] This risk has supported dose labeling recommendations for some drugs, such as intravenous voriconazole, even though the clearance of the active pharmaceutical ingredient is not dependent on GFR.[29] The effects of drugs or drug excipients on subject renal function, unlike the effects of renal function on drug PK, are often difficult to quantify in short-term clinical trials but, nonetheless, represent an important safety consideration in drug development.

Figure 1 highlights the different approaches taken by industry pharmacometricians to evaluate the effect of renal function on the PK of CZA, DLX, and M/V. The population PK

model of CZA used eCrCL to model renal function, which is consistent with the use of this equation throughout its clinical program.[10] The population PK model of DLX was developed using a modified C-G equation calculated using the lesser of ideal and actual body weight and normalized to BSA.[11] This modified C-G equation was not used for subject enrollment or stratification in any clinical trials of DLX. The M/V population models were constructed using the MDRD equation to model all levels of eGFR despite the known limitations of this estimate in subjects with normal or near normal renal function.[12]

Regulators. The use of both the C-G and MDRD equations in drug development increases the burden placed upon regulators when reviewing new drug applications (NDAs). The clinical pharmacology and biopharmaceutics review relies heavily on the assessment of pooled PK data from healthy subjects and patients both with and without renal impairment. Simulations using the population PK model are an integral method used to explore exposure-efficacy and exposure-toxicity relationships in special populations under-represented in clinical trials, including those with renal impairment. Because both the C-G and MDRD equations may be used in different clinical trial phases for the same investigational drug, regulators are frequently forced to consider the impact of different estimates of renal function on models and simulations.

In the review of DLX, the FDA assessed the relationship between various permutations of the C-G and MDRD equations using pooled Phase 3 data.[11] This analysis demonstrated a high correlation between the modified C-G equation used by the sponsor and MDRD equation (r = 0.92), but poor correlation between the modified and standard C-G estimates (r = 0.61). Because of the sponsor's modified C-G equation appeared to correlate

better with the MDRD equation than the standard C-G, the FDA reviewer re-analyzed the population PK data using the MDRD equation, which was eventually incorporated into the final product label.[11]

The FDA review of M/V highlights a different challenge to regulators due to variable methods of assessing renal function. The sponsor proposed a different renal dosing scheme for the product label than that used in the Phase 3 trial based on a probability of target attainment analysis performed using simulations derived from the population PK model.[12] These simulations were based on the assumption of a uniform distribution of eCrCL and bootstrapped covariate values obtained from the Phase 3 population. For the simulations, eCrCL was normalized to BSA and input as eGFR into the population model. Therefore, although the population model was built using the MDRD equation, the simulations which informed the final labeled dosing were performed using the C-G equation normalized to BSA. However, among subjects enrolled in the Phase 3 program of DLX, the correlation between the BSA-normalized C-G and MDRD estimates was 0.86.[11] Although normalizing eCrCL to BSA produces units equivalent to eGFR, these estimates of renal function are not interchangeable.

Clinicians and Health Systems. The complexity underlying the current practice of assessing renal function in clinical trials is not communicated to clinicians and health systems. These "end users" of drug dosing information receive only the final recommendations contained within the product label. This information must then be integrated into renal dose adjustment policies and protocols within the health system, which are intended to apply universally to all drugs requiring renal adjustment. The majority of

electronic health systems present renal function as eGFR calculated using the MDRD equation, which likely reflects the utility of the MDRD equation in staging CKD more than its applications to drug dosing.[30]

Integration of newly-approved drugs into existing renal dosage adjustment protocols may necessitate more complicated branching logic in electronic health systems or increased clinician awareness of the equations underlying labeled dose adjustments for individual drugs. Additionally, because the C-G equation is not recommended for staging CKD, an estimate of eGFR will need to be relayed to clinicians regardless of its utility in drug dosing. The most useful output for the electronic health system would be a value that is both useful for staging CKD and quantifying the entire distribution of patient renal function. However, given that the majority of renal dose adjustments of currently available drugs are based on the C-G equation, transition to any new estimate of renal function will need to be applicable to existing drugs on the market.

THE FORK IN THE ROAD

"When you come to a fork in the road, take it"- Yogi Berra

The current paradigm for assessing renal function in drug development introduces unnecessary heterogeneity in approaches to drug dosing in renal impairment. This is a complex problem and a true solution is unlikely as long as Scr remains the primary renal biomarker used in clinical practice. These inadequacies of Scr are well documented and include high inter-individual variation in production (diet, muscle mass) and elimination (tubular secretion) across the population.[31] Although, alternate biomarkers perform better than Scr in some settings, such as early detection of acute kidney injury, their overall clinical

utility, standardization, and reimbursement remain to be defined.[32] This multi-role application of Scr as a marker of renal function, renal injury, and drug dosing forces retention of this biomarker as the standard for classifying CKD and determining drug dosing in the near future.

The C-G and MDRD equations recommended by the FDA have multiple limitations impacting all users within the drug development and medication use systems. The C-G equation was determined by linear regression of only 7 data points representing mean measured creatinine excretion for male veterans averaged over decade intervals of age.[4] The use of measured CrCL as the reference method for this equation leads to over-prediction of true GFR due to tubular secretory clearance of creatinine and the bias inherent to development prior to creatinine standardization in clinical laboratories.[14] Indeed, the use of IDMS-traceable serum creatinine values in clinical laboratories today increases the inaccuracy of C-G eCrCL as this equation cannot be re-expressed for standardized serum creatinine values.[14] The MDRD equation, re-expressed for standardized creatinine values, demonstrates reduced bias relative to the C-G equation in subjects with renal impairment but is limited by systematic under-prediction of true GFR in subjects with normal or near-normal renal function.[6, 14] Additionally, the use of BSA-normalized eGFR values for subjects with non-standard body size leads to error in the prediction of the true absolute GFR underlying drug elimination.

We reviewed labels for new drugs approved by the FDA between 2015 and 2017 in order to assess the equations used to inform dosing recommendations in patients with renal impairment. New drug approvals for each year were obtained from the FDA website (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/). Approved product labeling was reviewed for each of the approved drugs, and supporting regulatory

review documents available within the public domain were referenced in cases where the equation underlying dosing recommendations in renal impairment was not explicitly stated. Dosing recommendations comprised both labeled dose reductions for renal impairment as well as labeled information confirming that no dose adjustment was required in renal dysfunction, as defined by a specified estimate of renal function. Drugs without dosing recommendations based on estimated renal function were excluded; therefore, the denominator for each year consists of all drugs approved during that year with dosing recommendations based on renal function.

In 2015, 24 of 29 (82.8%) approved drug labels included assessment of patients with renal impairment based on the C-G equation. In 2016, 7 of 10 (70.0%) labels were based on the MDRD equation, and in 2017 similar proportions of newly approved drug labels referenced the C-G (8/15, 53.3%) and MDRD (7/15, 46.7%) equations, respectively. Regardless of magnitude, there is a trend towards increasing use of the MDRD equation relative to C-G for drug dosing. This shift is resulting in discordant equation use for drugs within classes, as highlighted by delafloxacin (fluoroquinolones) and meropenem/vaborbactam (carbapenems). It is clear that the extended time horizon from design of Phase 1 studies to FDA approval creates a significant delay between implementation of guidance to industry and impact on approved drugs. Therefore, it is even more urgent that regulators address the existing limitations of current guidance and adapt quickly to improvements in the state of the art of renal function assessment.

Given the imprecision of all serum creatinine-based models for the estimation of renal function, it seems prudent to enroll and stratify the small number of subjects included in dedicated Phase 1 renal impairment studies using an exogenous measure of GFR. This is in line with the current recommendations from the EMA as well as a policy statement from

experts convened by Kidney Disease: Improving Global Outcomes (KDIGO).[7, 33] While measuring GFR using exogenous markers is impractical in later phase clinical trials, it can be performed in the relatively small sample of heathy subjects studied during Phase 1. This practice will ensure that the limited dedicated PK data from patients with renal impairment will be based on a "gold standard" reference value and reduce the risk for misclassification.

Estimates of GFR are required to screen patients for enrollment in Phase 2 and 3 trials and to inform pooled analyses of PK data from the entire clinical program. In our opinion, the CKD-EPI equation addresses many of the limitations of its predecessors and represents an opportunity to standardize renal function assessment across drug development.[34] First, the CKD-EPI equation was validated on pooled data from studies with exogenous measures of GFR representing the entire distribution of renal function.[34] Therefore, the CKD-EPI equation retains the advantage in precision of the MDRD equation without the systematic bias at normal or near-normal values of eGFR making it a useful measure for enrollment and pooled data analysis. Second, the CKD-EPI equation can be used both to stage CKD and determine drug dosing, which makes it a more optimal measure for implementation in clinical laboratory reporting and electronic health systems. However, because drug elimination is often related to absolute, rather than BSA normalized, glomerular filtration rate; eGFR values may need to be de-normalized for drug dosing as recommended by the EMA.[7] A comparison of the three primary serum creatinine-based models for estimating renal function is presented in Table 2.

The CKD-EPI equation has demonstrated utility in predicting drug pharmacokinetics and informing dosing. Studies with the aminoglycosides, compounds that serve as excellent probes of glomerular filtration, have verified that the CKD-EPI equation is likely to be more precise than either the C-G and MDRD equations.[35, 36] The CKD-EPI equation has also

shown to be relevant for stratification of risk when dosing edoxoban in patients with good renal function.[37] Also, the CKD-EPI estimates of renal function led to concordant dosing recommendations of antiretroviral dosing in a French cohort of patients with HIV.[38] Notably, these studies have demonstrated that concordance is best using absolute (mL/min) rather than BSA normalized (mL/min/1.73m^2) estimates of renal function.

The CKD-EPI equation represents an incremental improvement in the assessment of renal function rather than a fundamental paradigm shift. All the limitations of Scr as a biomarker still apply to the CKD-EPI equation although newer versions of this equation incorporating cystatin C, with or without Scr, have also been developed.[39] Additionally, the effect of race in the CKD-EPI equation has been found to vary across racial and ethnic groups distinct from those used to train the original model.[40-42] The current race factor appears to be appropriate in Black Americans or people of European descent; however, it may not be valid in black African or Asian populations.[40-42] Re-expression of the CKD-EPI equation using the ratio of measured serum creatinine to a race- and sex-based population median value may improve use of this equation in settings outside of the United States and Europe.[43] Although more research is needed to validate this approach, it should be recognized that this variable can be accounted for in bridging studies dedicated to dose optimization across race and ethnicity.

CONCLUSION

The current regulatory guidance for the assessment of renal function in drug development is increasing heterogeneity in study design and data analysis for investigational therapeutics. Both the C-G and MDRD equations are used across drug development without a

predominant approach advocated by regulatory agencies. The CKD-EPI equation provides an incremental improvement over both the C-G and MDRD equations and offers a method to standardize the assessment of renal function in clinical trials, pooled data analysis, and clinical practice. Given the significant time horizon between early phase PK studies and regulatory approval of novel therapeutics, regulatory agencies should update current guidance to industry in line with the evolving state of the art in the assessment of patient renal function. Incorporation of measured GFR in Phase I studies with later assessment via the CKD-EPI equation is a necessary consideration for regulators to avert the expected discordance with use of the C-G and MDRD equations.

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Figure 1: Assessment of renal function throughout the drug development process for the three systemically active antibiotics approved by the FDA since 2015. Abbreviations: C-G, Cockcroft-Gault equation; C-$G_{IBW,BSA}$, Cockcroft-Gault equation calculated using the lesser of ideal and actual body weight and normalized to body surface area; MDRD, Modification of Diet in Renal Disease equation; PK, pharmacokinetic

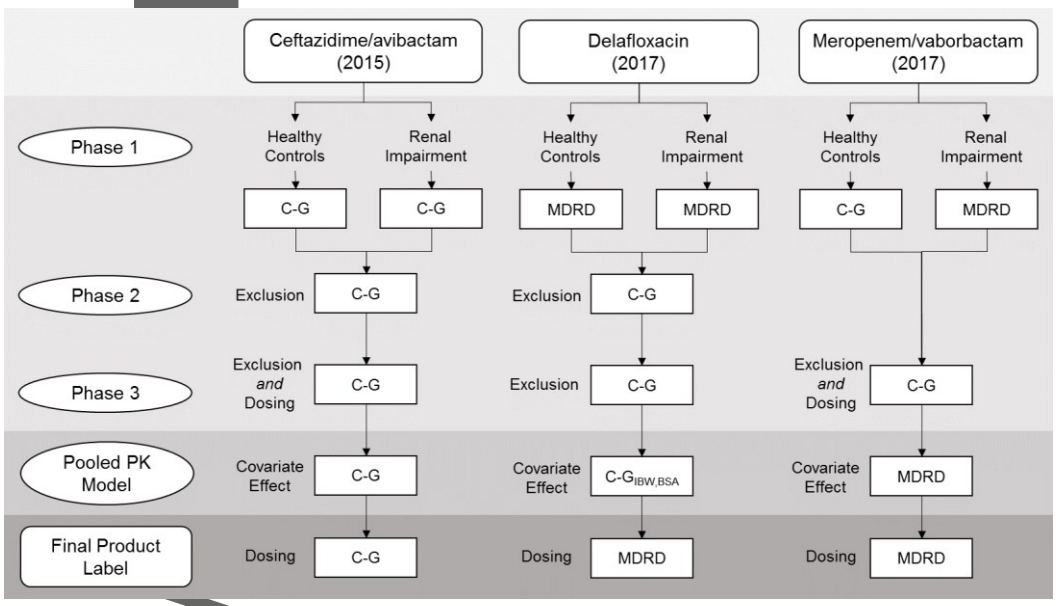

Table 1: Discordant Classification of Subjects Enrolled in a Phase I Study of Delafloxacin using the Cockcroft-Gault and Modification of Diet in Renal Disease Equations

Group	eGFR or eCrCL[a]	MDRD			Cockcroft-Gault		
		N	Geometric LS Mean AUC_{0-t}[b]	AUC Ratio (90% CI)	**N**	Geometric LS Mean AUC_{0-t}[b]	AUC Ratio (90% CI)
Healthy subjects	> 80	**8**	23.12	*Reference*	**14**	25.55	*Reference*
Mild Impairment	51-80	**8**	30.51	1.32 (0.93, 1.87)	**7**	34.97	1.37 (0.99, 1.89)
Moderate Impairment	31-50	**8**	38.20	1.65 (1.17, 2.35)	**8**	48.39	1.89 (1.39, 2.58)
Severe Impairment	≤ 30	**8**	46.57	2.01 (1.42, 2.86)	**3**	39.87	1.56 (1.00, 2.43)

Abbreviations: MDRD, Modification of Diet in Renal Disease equation; eGFR, estimated glomerular filtration rate calculated using the MDRD Equation; eCrCL, creatinine clearance calculated using the Cockcroft-Gault equation; AUC_{o-t}, area under the concentration time curve [AUC] from time 0 to the last quantifiable concentration; CI, confidence interval

[a]eGFR was measured in units of mL/min/1.73 m^2 while eCrCL was measured in units of mL/min

[b]AUC values were obtained following a single intravenous dose of 300 mg and are presented in units of µg*h/mL

Data from references 11 and 19

Table 2: Comparison of the Three Primary Serum Creatinine-based Equations Used to Estimate Renal Function

	Cockcroft-Gault	MDRD	CKD-EPI
Study Characteristics			
Year	1976	1999 (6 variable) 2006 (4 variable)	2009
Reference Method	24-hour creatinine clearance	^{125}I-iothalamate clearance	^{125}I-iothalamate clearance
Enrollment (Males / Females)	249 / 0	983 / 645	3113 / 2391
Patient Renal Function[a]	73 ± 37 mL/min	40 ± 21 mL/min/1.73 m^2	68 ± 40 mL/min/1.73 m^2
Comparison of Equations			
Variables	age, sex, serum creatinine, weight	age, sex, serum creatinine, race	age, sex, serum creatinine, race
Developed using an exogenous measure of GFR?	NO	YES	YES
Developed or re-expressed for use with IDMS-traceable serum creatinine?	NO	YES	YES
Valid across the full spectrum of renal function?	YES	NO	YES

Currently recommended for staging of CKD?	NO	YES	YES
Currently recommended for drug dosing by regulatory agencies?	YES	YES	FDA: NO EMA: YES

Abbreviations: MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD, chronic kidney disease; IDMS, isotope dilution mass spectrometry; GFR, glomerular filtration rate; FDA, United States Food and Drug Administration; EMA, European Medicines Agency

[a] Data presented as mean ± standard deviation