

May 21, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2010–D–0133: Revised Draft Guidance for Industry on Pharmacokinetics in Patients With Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling; Availability

Dear Ladies and Gentlemen,

On behalf of the American Society of Nephrology (ASN), a not-for-profit organization of 11,000 physicians and scientists dedicated to helping nephrologists provide the highest quality of patient care possible, thank you for the opportunity to provide comment on the Food and Drug Administration's (FDA) Revised Draft Guidance for Industry on Pharmacokinetics in Patients With Impaired Renal Function.

ASN is committed to promoting excellence in the care of patients with kidney disease and to promulgating innovative research related to renal disease. The society appreciates FDA's willingness to collaborate with the nephrology community to address the important issues and challenges related to assessing the influence of renal impairment on the pharmacokinetics of an investigational drug.

ASN's Acute Kidney Injury Advisory Group, Chronic Kidney Disease Advisory Group, and Dialysis Advisory Group have reviewed and discussed the FDA revised draft document for industry "Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling." In general the advisory groups believe this is an important and well-written document. In addition, we submit the following recommendations and comments on the draft guideline.

We suggest that the introduction include a general statement regarding the magnitude of incident and prevalent chronic kidney disease (CKD) and acute kidney injury (AKI) populations in the U.S. to emphasize the scope of the disease burden and establish that kidney disease is a serious public health threat. We recommend that the introduction highlight that more than ten percent of the general U.S. population has significant CKD—a substantial portion of the industry's market. Consequently, pharmacokinetic (PK) studies should not be ignored but rather rigorously studied in persons with CKD who are not on dialysis, as well as in the end-stage renal disease (ESRD) and AKI populations.

Pharmacokinetic Studies in CKD, ESRD, and AKI

In the discussion of pharmacokinetics it is essential to include the effects of AKI. The current document focuses almost exclusively on impaired GFR in chronic kidney disease (CKD) and End Stage Renal Disease (ESRD). This important distinction should be considered as patients with AKI have a higher acuity and often their kidney function is not in a steady state. Therefore, the standard formulas used to calculate eGFR cannot be used to accurately assess the level of kidney function in AKI patients. In addition, the vascular permeability of patients with AKI can be altered, leading to changes in the volume of distribution of drugs. Similarly, the non-renal clearance of drugs in AKI has been shown to differ from that in CKD, leading to different PK parameters despite similar levels of kidney function. Thus, drugs that are likely to be used in the setting of AKI (particularly antibiotics) need to be evaluated to ensure that the differences in PK parameters in the acute and chronic settings are not clinically relevant.

We suggest the document more clearly state that drug PK studies should be conducted in pre-dialysis CKD patients with a steady state of renal function. For example, PK studies should only be performed in patients in whom plasma creatinine measurements on two separate days are similar.

The guidance document states that in “drugs and metabolites with a relatively low extent of plasma protein binding (e.g., extent of binding less than 80%), alterations in binding due to impaired renal function are small in relative terms” (page 5, line 197). This is incorrect. For example, theophylline binding (normally 60% bound to protein) and methotrexate (normally 40% bound to protein) are reduced by 20 and 15%, respectively, in patients with kidney failure (Vanholder et al, KI, 1988, 33, 996-1004).

Renal Replacement Therapy

While recognizing the importance of fully examining issues related to drug clearance in intermittent hemodialysis (IHD), we believe that the guidance document contains inadequate discussion of drug clearance in continuous renal replacement therapy (CRRT). The document proposes to extrapolate *in vitro* data and available data from patients on IHD to estimate appropriate drug dosing recommendations during CRRT until PK data from clinical studies of CRRT are available. However, we suggest that the FDA specify that all dialysis PK studies include both IHD and CRRT. We propose that FDA base CRRT-related recommendations on a paper by Mueller and Smoyer (Clinical Pharmacology and Therapeutics 86:479-482, 2009) with the caveat that based the results of the VA/NIH Acute Renal Failure Trial Network (ATN) Study (N Engl J Med 2008;359:7-20) and the RENAL Study (N Engl J Med 2009;361:1627-1638), it is difficult to justify continued use of CRRT dosing at 35 ml/kg/hr, and therefore recommend that FDA support the use of a 20-25 ml/kg/hr effluent flow for CRRT in the final guidance document.

FDA may also wish to consider including discussion of the impact of residual kidney function in patients with CKD/ESRD and AKI. This is especially true for AKI when the serum creatinine is rising or falling.

Additionally, the guidance document should make a clear distinction between the different dialysis therapies: hemodialysis (HD), peritoneal dialysis (PD), and CRRT. Although FDA addresses some alternative dialysis procedures, we suggest that the guidance document also discuss daily dialysis, and long, slow hemodialysis procedures—for instance, nocturnal dialysis in ESRD, and extended daily dialysis (EDD) or sustained low-efficiency dialysis (SLED) in AKI. Further, note that there may also be differences in drug clearance rates between different dialysis strategies, such as diffusion, convection, daily dialysis, and long extended dialysis. FDA may wish to highlight the potential for these differences in the guidance document and encourage industry to bear them in mind when designing studies of new pharmaceutical products in patients with impaired kidney function.

eGFR and Creatinine Clearance

We are concerned that the draft guidance document implies that estimated glomerular filtration rate (eGFR) is equivalent to creatinine clearance. Creatinine clearance significantly overestimates GFR. Therefore, the manuscript should state clearly that eGFR as determined by the Modification of Diet in Renal Disease (MDRD) equation or other measures are not equivalent to creatinine clearance estimated by the Cockcroft-Gault (CG) formula. Historically, since most PK studies were performed with CG, inclusion of CG data is reasonable. However, new PK studies should be based on more accurate equations, such as the MDRD or the CKD-EPI. Table 2 should be changed to reflect this point.

Because we believe classification of CKD stages should be based on eGFR rather than creatinine clearance, we suggest that FDA may wish to consider omitting the last column in Table 1 “Classification of Renal Function Based on Estimated GFR (eGFR) or Estimated Creatinine Clearance (CLcr).”

The MDRD equation cited on page 7 of the guidance document is incorrect. The number should be 186, rather than 175.

Finally, while complete collection of the entire dialysate is optimal, alternate techniques utilizing multiple, timed aliquots collections is equally viable and, in some cases, more economical.

Pediatric Considerations

The new GFR estimating equation developed in the CKiD study should be used when addressing the needs of children with CKD. The equation is used when the creatinine is measured using the enzymatic technique. It has not been validated in patients with normal kidneys. The older Schwartz formula, which was applied to premature infants, neonates, children and adolescents, was based on creatinine values determined with the Jaffe technique and significantly overestimates GFR when used with enzymatic creatinine values. The newer formula has not been validated in premature infants and neonates with CKD.

On behalf of ASN, thank you for your willingness to consider our comments for the draft guidance document. Our members are committed to providing the best possible care and appreciate the FDA's efforts to ensure the safe and appropriate study and use of pharmaceutical products used in the treatment of patients with impaired renal function. We would be pleased to discuss these comments and recommendations with the agency if it would be helpful.

Again, thank you for your time and consideration. To discuss these comments, please contact Paul Smedberg at psmedberg@asn-online.org or at (202) 416-0646.

Sincerely,



Sharon Anderson, MD, FASN
President