Influence of Kidney Disease on Drug Disposition: An Assessment of Industry Studies Submitted to the FDA for New Chemical Entities 1999–2010

Gary R. Matzke, PharmD, FCP, FCCP, FASN1, Thomas C. Dowling, PharmD, PhD, FCCP2, Samantha A. Marks, PharmD1, and John E. Murphy, PharmD, FCCP, FASHP3

Abstract

In 1998, the United States Food and Drug Administration (FDA) released the first guidance for industry regarding pharmacokinetic (PK) studies in renally impaired patients. This study aimed to determine if the FDA renal PK guidance influenced the frequency and rigor of renal studies conducted for new chemical entities (NCEs). FDA-approved package inserts (APIs) and clinical pharmacology review documents were analyzed for 194 NCEs approved from 1999 to 2010. Renal studies were conducted in 71.6% of NCEs approved from 1999 to 2010, a significant increase over the 56.3% conducted from 1996 to 1997 (P = .0242). Renal studies were more likely to be completed in highly renally excreted drugs (fe/C21 > 30%) compared with drugs with low renal excretion, fe < 30% (89.6% vs 65.8%, P = .0015). PK studies to assess the impact of dialysis were conducted for 31.7% of NCEs that had a renal study: a greater proportion of high fe NCEs were studied (44.2% vs 26.0%, P = .0335). No significant change in frequency or rigor of PK studies was detected over time. The majority of NCEs (76.3%) with a renal study provided specific dosing recommendations in the API. The adoption of the 1998 FDA guidance has resulted in improved availability of PK and drug-dosing recommendations, particularly for high fe drugs.

Keywords

new chemical entity, drug dosing, kidney function, pharmacokinetics, dialysis

The pharmaceutical industry has been charged with the responsibility to determine the relationship between kidney function and the pharmacokinetics (PK) of new drugs and to propose dosage recommendations, to minimize the incidence of adverse events and optimize therapeutic outcomes, to regulatory agencies. Prior to 1998, there was no structured regulatory agency expectation of when, how, and for which drugs such studies should be conducted.1 In fact, much of the information on the PK of drugs in patients with chronic kidney disease (CKD), including patients receiving renal replacement therapy (RRT) resulted from clinician-initiated postmarketing studies. These studies often employed small numbers of patients and resulted in the publication of inconsistent or conflicting dosage adjustment recommendations.2–4 These PK evaluations and the resultant drug dose adjustment recommendations for CKD patients have been the topic of several articles.5–8 Many of the critical questions regarding drug use in patients with renal insufficiency have recently been reviewed by an expert working group convened by Kidney Disease Improving Global Outcomes (KDIGO).9 Specific issues include identifying the most accurate and reliable index of “kidney function” for drug dosing and determining which study design elements are essential to reliably quantify the influence of chronic kidney disease, acute kidney injury, and renal replacement therapies on drug PK. These recommendations as proposed impact clinicians, scientists, and regulatory agencies.

In 1998, the United States Food and Drug Administration (FDA) released the first formal regulatory agency guidance regarding PK in patients with impaired renal function. This guidance document provided recommendations regarding when studies of PK in patients with impaired renal function should be performed, the design and conduct of such PK studies in CKD and dialysis patients, and the analysis and reporting of results.10 It also

1Department of Pharmacotherapy and Outcomes Science, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, USA
2Department of Pharmacy Practice, College of Pharmacy, Ferris State University, Grand Rapids, MI, USA
3Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, Tucson, AZ, USA

Submitted for publication 28 May 2015; accepted 30 July 2015.

Corresponding Author:
Gary R. Matzke, PharmD, FCP, FCCP, FASN, FNAP, FAAAS, Department of Pharmacotherapy and Outcomes Science, School of Pharmacy, Virginia Commonwealth University, PO Box 980533, 1112 E. Clay St, Richmond, VA 23298
Email: gmatzke@vcu.edu

The Journal of Clinical Pharmacology 2015, XX(XX) 1–9
© 2015, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.604
presented a framework for the inclusion of PK information and drug dosage regimen recommendations into FDA-approved prescribing information (FDA-approved package inserts [APIs]). The impact of the introduction of this guidance on the frequency of renal studies and the inclusion of dosage adjustment recommendations in FDA-APIs was assessed by Zhang et al for 94 new drug applications (NDAs) for small-molecule new chemical entities (NCEs) approved from January 2003 to July 2007.11 The authors noted a small increase in the proportion of NCEs for which renal studies were conducted prior to NDA or supplemental NDA approval of 56.3% before guidance versus 57% for NDAs approved in 2003–2007. However, the frequency of renal dosage adjustment language inclusion in FDA-APIs declined from 79% to 41%.

The current study was designed to determine if the frequency and rigor of renal studies changed over time after the introduction of the FDA renal PK guidance in 1998. The specific objectives were (1) to determine the difference in the number and type of renal studies conducted over the first 12 years (1999–2010) following the FDA renal guidance, (2) to compare the completion of renal studies, dialysis studies, and full renal studies between drugs with a high fraction eliminated renally unchanged (fe) and drugs with a low fe, (3) to assess the frequency of PK studies conducted in patients with acute kidney injury (AKI) and those receiving continuous renal replacement therapy (CRRT), and (4) to analyze the guidance’s impact on the specificity of dosage recommendation language in FDA-APIs.

Methods
This study was a retrospective analysis of publically available documents; therefore, institutional review board approval was not required. Informed consent was not required because this is a literature review. The FDA-APIs and FDA clinical pharmacology review documents (FDA-CPRs) of the 299 drugs approved between January 1, 1999, and December 31, 2010, were reviewed. The data from 47 local-acting medications, 47 entities approved through the biologic license application pathway, and 11 drugs that were approved but no longer on the market in the United States at the time of final data collection (June–August 2011) were excluded from the analysis. Thus, the final data set consisted of 194 NCEs for which new drug applications (NDAs) were approved by the FDA from 1999 to 2010 (Figure 1).

Data Collection
For each NCE included in the study, the most recently available FDA-APIs and FDA-CPRs were examined. All documents were publically available on the FDA website, and accessed through the Drugs@FDA search engine (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

Figure 1. Summary of renal studies performed on new chemical entities approved from 1999 to 2010.
The fraction of the drug eliminated renally unchanged in subjects with normal renal function ($f_e$), the presence of a renal study, study design (single dose, multiple dose, or population PK), CKD patient populations evaluated (normal, mild, moderate, severe, and end-stage renal disease), and the findings of a dialysis study, if one was conducted, were recorded. A study was considered “full” if it evaluated all CKD patient populations. The following additional study parameters were recorded if available: number of subjects enrolled in each renal function group, data analysis approach employed by the entity submitting the NDA, and relationship of PK parameters to creatinine clearance.

Evaluation of Renal Drug Dosing Information in FDA-APIs
The pharmacokinetic data available in FDA-APIs and FDA-CPRs were used to categorize the relationship between the drugs’ PK evidence and proposed dosing recommendations. If a significant change in PK was present in patients with any degree of renal impairment, the study was categorized as showing a PK effect (E). If no significant change in PK was noted in the renal study the study was categorized as showing “no effect” (NE). If the FDA-API recommended dose adjustments in patients with any degree of renal impairment, the drug was categorized as requiring an adjustment (A), whereas labels that stated no adjustment to be necessary and those that did not mention an adjustment specifically were categorized as not requiring an adjustment (NA). FDA-APIs that did not include directions for drug use in patients with AKI or CKD were coded as “no language” (NL). Each FDA-API was thus categorized as having “PK effect and adjustment necessary (EA),” “PK effect but no adjustment recommended (ENA),” “no PK effect, no adjustment recommended (NENA),” or “no language provided (NL).”

The API was categorized as being specific or nonspecific based on their conveyance of essential information to health care providers. Five qualities were identified as indicators of specific labels: (1) tabulation of changes in PK parameters (ie, clearance), (2) specific dosage adjustment language presented (ie, dosage reduction or prolongation of dosing interval), (3) inclusion of study design characteristics, (4) statement of the impact of dialysis on drug concentrations and/or dosage recommendations for dialysis patients (if applicable), and (5) clearly defined categories of renal insufficiency for which dosage adjustment is necessary (eg, CrCl $<30$ mL/min vs “moderate” dysfunction). Specific labels were defined as those that included at least 3 of these qualities.

Data Analysis
 Drugs were grouped according to year of approval (1999–2001, 2002–2004, 2005–2007, 2008–2010) and stratified on the basis of percent $f_e$ in subjects with normal renal function (low, $<30$%; high, $\geq30$%). Frequencies and percentages were used to characterize the number and type of renal studies, frequency of dialysis studies, relationship between PK effect and dose adjustment, and specificity of the API language. Results of this analysis were compared with 2 previous studies using chi-square tests. Differences in frequency and type of study design between high- and low-$f_e$ groups and across the 4 periods were tested using chi-square and Fisher’s exact tests. An a priori significance level of .05 was used for the analysis. Statistical tests were conducted using SAS v. 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results
Renal PK studies were conducted for 71.6% of the 194 NCEs approved during the 12-year study period (Table 1). This frequency is significantly higher ($P = .0242$) than the 56.3% reported by Ibrahim et al from 1996 to 1997, prior to the introduction of the FDA guidance. The 2003–2007 evaluation by Zhang et al reported that the percent of renal study conduction had not increased significantly from the preguidance era. ($56.3\%$ vs $57\%$) There was, no significant difference in the frequency with which renal PK studies were conducted over the four 3-year intervals from 1999 to 2010 ($P = .7099$). The percentage of NCEs that had a renal study conducted ranged from a low of 66% in 2002–2004 to a high of 75.5% in 2008–2010 (Table 2).

The predominant drug classes represented in the 194 NCEs evaluated are depicted in Table 1 along with the number of those that had a renal study. Oncology and antiretroviral agents were least often studied (56.3% and 61.5%, respectively), whereas renal studies were conducted for greater than 90% of anticoagulant/antiplalet, psychiatric, and diabetes agents (Table 1).

Renal PK studies were significantly more likely to be completed for high-$f_e$ NCEs (89.6%) versus low-$f_e$ NCEs (65.8%); $P < .0015$ (Table 2). The type of renal PK study

Table 1. NCEs and Renal Studies by Drug Class (n = 194)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>NCEs</th>
<th>Renal Studies</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic agents</td>
<td>12</td>
<td>11</td>
<td>91.7</td>
</tr>
<tr>
<td>Antidepressants/antipsychotics</td>
<td>17</td>
<td>15</td>
<td>98.2</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>21</td>
<td>18</td>
<td>85.7</td>
</tr>
<tr>
<td>Antivirals</td>
<td>13</td>
<td>8</td>
<td>61.5</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>21</td>
<td>17</td>
<td>81.0</td>
</tr>
<tr>
<td>CNS agents</td>
<td>21</td>
<td>19</td>
<td>90.5</td>
</tr>
<tr>
<td>Contrast/diagnostic agents</td>
<td>8</td>
<td>5</td>
<td>62.5</td>
</tr>
<tr>
<td>Gastrointestinal agents</td>
<td>9</td>
<td>8</td>
<td>88.8</td>
</tr>
<tr>
<td>Genitourinary agents</td>
<td>9</td>
<td>5</td>
<td>62.5</td>
</tr>
<tr>
<td>Oncologic agents</td>
<td>32</td>
<td>18</td>
<td>56.3</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
<td>13</td>
<td>41.9</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>139</td>
<td>71.6</td>
</tr>
</tbody>
</table>
that was completed during each of the 3-year evaluation periods for both high- and low-\(fe\) NCEs is depicted in Table 3. Figures 2A and 2B present the proportion of renal study types conducted among the 146 and 48 low and high \(fe\) NCEs. A trend toward conduction of more full studies during the 12-year period is evident for the high-\(fe\) NCEs (Figure 2A); however, this difference was not statistically significant \((P = .4426)\). In the low-\(fe\) NCE group, full studies never exceeded 30% of all renal studies in a given 3-year period, whereas in the high-\(fe\) group the frequency was never less than 45%. Specific language regarding PK evaluation among patients with AKI was not included in FDA-CPRs or FDA-APIs for any of the NCEs.

PK studies to assess the impact of hemodialysis (HD), peritoneal dialysis (PD), and/or CRRTs were done for 44 of the 194 NCEs evaluated (22.6%); see Table 3. Forty-four percent of high-\(fe\) NCEs with a renal study also had a dialysis study conducted, compared with only 26% of the low-\(fe\) NCEs \((P = .0035; \text{Table 3, Figure 2A,B})\). HD was the predominant mode of RRTs evaluated: only 4 studies evaluated PD and 1 study CRRT. The number of subjects in the dialysis evaluations were small, usually 6 or less, and the specifics of the dialysis procedure (dialyzer utilized, blood or dialysate flow rates, and duration of the procedure) were generally not delineated in the FDA-APIs or the FDA-CPRs. The fraction of the drug removed during the dialysis procedure and clearance by dialysis were only reported for 25 and 11 NCEs, respectively. Specific dosage recommendations for patients undergoing chronic HD were documented in the FDA-APIs for 79.5% of the 44 NCEs that had a dialysis study done. Details of all dialysis studies are available online in Supplemental Table S1.

The FDA-APIs provided dosage information for patients with renal impairment for 95.7% of NCEs that had a renal PK study done (Table 3). No significant change in the pharmacokinetics and no dosage adjustment were recommended in the FDA-APIs for 34.5% of the NCEs. This was a finding predominantly confined to NCEs with a low \(fe\) \((N = 46)\), and most \((n = 32)\) were noted in the 1999–2001 and 2002–2004 intervals. Significant PK changes were identified for 45.8% of low-\(fe\) NCEs and 95.4% of high-\(fe\) NCEs \((P \leq .0001)\). A significant alteration in the NCE PK as well as a dosage recommendation was reported in 74.4% of high-\(fe\) NCEs’ FDA-APIs, but only 32.2% of low-\(fe\) NCEs \((P < .001)\). Some examples of specific renal dosing recommendations in FDA-APIs are provided in Table 4.\(^{12-16}\) The specificity of the dosage recommendations did not improve over time and did not significantly differ between the high-\(fe\) NCEs, 83.7%, and the low-\(fe\) NCEs, 72.9% \((70 \text{ of } 96); P = .1664; \text{Table 3})\.

**Discussion**

The 1998 FDA guidance addressed the fundamental questions of which drug characteristics warrant the conduction of a renal study, when and how renal studies should be conducted and analyzed, and how the results should be incorporated into APIs.\(^{10}\) The pharmacokinetic study options were prioritized with limited studies (ie, those employing single-dose administration in those with normal renal function and those with end-stage renal disease [ESRD] who were not yet receiving maintenance dialysis recommended in some settings). Single-dose administration to 4–5 groups of patients with renal function ranging from normal, mild, moderate, to severe and ESRD was preferred but not mandated when studies were suggested. The completion of a study in patients receiving maintenance dialysis was recommended whenever “the drug was likely to be used in that patient population.” Recommendations for incorporation of information derived from a renal study into an API were also proposed for the first time.

The results of this investigation demonstrate that the 1998 FDA renal guidance for the assessment of the pharmacokinetics and dynamics was associated with an increase in the frequency with which drugs were evaluated and increased the rigor of the studies conducted in patients with renal insufficiency. The percent of NCEs that had a renal PK study conducted increased significantly \((P = .0242)\), from 56.3% of NCEs in the preguidance period (1996–1997), to 71.6% in 1999–2010. (Table 2). The FDA guidance had a more positive impact than the 2003–2007 time frame data indicated.\(^{11}\) Renal studies were conducted significantly more
Table 3. Characteristics of Renal Studies and Dosing Adjustment Recommendation Language by Year

<table>
<thead>
<tr>
<th>Study type</th>
<th>Total (n = 139)</th>
<th>fe &lt; 30% (n = 96)</th>
<th>fe ≥ 30% (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Full</td>
<td>72 (51.8)</td>
<td>13 (44.8)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Limited</td>
<td>44 (31.7)</td>
<td>10 (34.5)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Pop PK</td>
<td>23 (16.5)</td>
<td>6 (13.6)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>44 (31.7)</td>
<td>10 (34.5)</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>73 (52.5)</td>
<td>10 (34.5)</td>
<td>13 (65.0)</td>
</tr>
<tr>
<td>Multidose</td>
<td>12 (8.6)</td>
<td>4 (13.7)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Both</td>
<td>8 (5.8)</td>
<td>1 (3.4)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Not reported</td>
<td>46 (33.1)</td>
<td>14 (48.3)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>PK effect</td>
<td>85 (61.2)</td>
<td>12 (41.4)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>Dose adjustment recommendations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>63 (45.3)</td>
<td>10 (34.5)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>ENA</td>
<td>22 (15.8)</td>
<td>2 (6.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>NENA</td>
<td>48 (34.5)</td>
<td>17 (58.6)</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td>NL</td>
<td>6 (4.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Specificity of dose recommendations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>106 (76.3)</td>
<td>20 (69.0)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>33 (23.7)</td>
<td>9 (31.0)</td>
<td>6 (26.1)</td>
</tr>
</tbody>
</table>

EA, pharmacokinetic effect demonstrated in renal study and dosage adjustment needed; ENA, effect, no dosage adjustment needed; NENA, no effect, no dosage adjustment needed; NL, no language in label pertaining to dosage adjustment needed.

*The percentage was calculated as the quotient of the number of the renal study type, study design, dose adjustment recommendation inclusion, and specificity of the dose recommendation relative to the number of renal studies conducted in the given period, which is listed in Table 2.
frequently (89.6% of the time) for those NCEs with a high fe compared with 65.8% for those NCEs with fe < 30% (Table 3).

The rigor of the renal studies varied among the high- and low-fe NCEs (Table 3). Full study designs were more common in the high-fe group in all 4 periods (range, 54.5%–85.7%) versus the low-fe group (range, 40%–52.2%). Full study designs were thus more frequently employed for high-fe NCEs, especially during the years 2005–2010, than previously reported by Zhang et al.11 The frequency with which full studies were completed in the low-fe NCEs remained persistently low. Population

Table 4. Renal Dosing Language and Study Design Elements in the FDA-API12–16

<table>
<thead>
<tr>
<th>Criteria for Specific Labels</th>
<th>Wording From Selected APIs That Exemplify Specificity</th>
<th>NCE Brand and Generic Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion of changes in PK parameters</td>
<td>“After administration of a single dose of 40 mg LATUDA to patients with mild, moderate, and severe renal impairment, mean Cmax increased by 40%, 92%, and 54% respectively, and mean AUC(0–∞) increased by 53%, 91%, and 2-times, respectively, compared to healthy matched subjects.”</td>
<td>Latuda (lurasidone HCl)</td>
</tr>
<tr>
<td>Specific dose-adjustment language</td>
<td>“…CrCl in mL/min may be estimated from serum creatinine (mg/dL) using the [Cockcroft-Gault] formula. Dosing adjustment regime for adult patients with impaired renal function: normal (≥80 mL/min): 500–1,500 mg every 12 hours, mild (50–80 mL/min): 500–1,000 mg every 12 hours, moderate (30–50 mL/min): 250–750 mg every 12 hours, severe (&lt;30 mL/min): 250–500 mg every 12 hours, ESRD patients using dialysis: 500–1,000 mg every 24 hours. Following dialysis, a 250–500 mg supplemental dose is recommended.”</td>
<td>Keppra (levetiracetam)</td>
</tr>
<tr>
<td>Inclusion of renal study characteristics</td>
<td>“A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment (N=8 per group)…classified on the basis of creatinine clearance as mild (≥50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (&lt;30 mL/min), as well as patients with end-stage renal disease on hemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula…”</td>
<td>Onglyza (saxagliptin)</td>
</tr>
<tr>
<td>Discussion of the impact of dialysis on PK and dosage recommendations</td>
<td>“A single 400 mg dose of Teflaro was administered to subjects with ESRD (n=6) either 4 hours prior to or 1 hour after hemodialysis (HD). The geometric mean ceftaroline AUCp&lt;inf&gt;∞&lt;/inf&gt; following the post-HD infusion was 167% higher compared to healthy subjects with normal renal function…The mean recovery of ceftaroline in the dialysate following a 4-hour HD session was 76.5 mg, or 21.6% of the administered dose. Dosage adjustment in patients with ESRD (defined as CrCl &lt;15 mL/min), including patients on HD…Recommended dosage regimen for Teflaro in end-stage renal disease including hemodialysis is 200 mg IV (over 1 hour) every 12 hours. Teflaro is hemodialyzable; thus Teflaro should be administered after hemodialysis on hemodialysis days.”</td>
<td>Teflaro (ceftaroline)</td>
</tr>
<tr>
<td>Clearly defined categories of renal insufficiency</td>
<td>“No dosage adjustment in necessary in patients with mild renal impairment (24-hr CrCl = 50–80 mL/min). The recommended dose in patients with moderate renal impairment (24-hr CrCl = 30–50 mL/min) is 50 mg per day. The recommended dose in patients with severe renal impairment (24-hr CrCl &lt; 30 mL/min) or end-stage renal disease is 50 mg every other day. Supplemental doses should not be given to patients after dialysis.”</td>
<td>Pristiq (desvenlafaxine)</td>
</tr>
</tbody>
</table>
PK studies were conducted more frequently in 2005–2010 in the low-fe group, whereas limited studies declined over the 12-year period in both fe groups. These data suggest that the pharmaceutical industry has embraced the guidance in a favorable fashion, at least with regard to the more frequent initiation of renal studies that are more rigorous for NCEs in the high-fe group. In contrast, among the low-fe NCEs no study was conducted 31%–39.5% of the time over the 12-year observation period. Limited studies declined in both NCE groups. Several recent reviews have focused on enrollment inclusion and exclusion criteria for CKD and dialysis patients, as well as the number of subjects who should comprise each renal function category.\textsuperscript{17–20}

The pharmacokinetic parameters were almost exclusively assessed following single-dose administration of the NCE (Table 3), and rarely was the methodology used to estimate the NCE pharmacokinetic parameters indicated in the API or FDA clinical pharmacology report. Thus, we were not able to assess if the noncompartmental methodology that is recommended in the guidance has been consistently used. In addition, the statistical approach to compare PK parameters is of critical concern. The utilization of analysis of variance to estimate the mean PK parameter values and 90% confidence intervals in categorical groups of patients that may be appropriate when a limited study design is employed is not optimal when a full study design is employed. When a full study design is employed, regression analysis to characterize the relationship between renal function and the NCE PK parameters is preferred. Although this approach is an improvement over categorical analysis, some have proposed that it does not yield a full pharmacokinetic profile of the NCE.\textsuperscript{17,18}

The results of the renal studies indicated the presence of significant PK changes for 45.8% of low-fe NCEs and 95.4% of high-fe NCEs (P \(\leq .0001\)). Dosage adjustment language for patients with CKD was recommended in the APIs for 70.5% and 74.4% of low- and high-fe NCEs, respectively, for which there was a significant change in PK parameters. Dosage recommendations tended to be made when there were significant PK changes; however, the presence of significant PK changes did not always result in dosage recommendations in the APIs.

The specificity and thereby the clinical utility of the drug dosage-adjustment language in the APIs has been raised as a concern in the past.\textsuperscript{21,22} During the time frame of the data collection for this analysis, the FDA regulations regarding labeling were modified by the enactment of the Physician Labeling Rule in 2006.\textsuperscript{23} Thus, detailed results of renal studies may appear in the PK subsection of the Clinical Pharmacology section as well as the Dosage and Administration or Use in Specific Populations subsection. The labeling language was deemed specific more often for high-fe versus low-fe NCEs; 83.7% versus 72.9%, respectively, across the 12 years of our analysis.

Currently more than 449 342 patients in the United States are receiving some variant of chronic RRT (408 711 hemodialysis and 40 631 peritoneal dialysis),\textsuperscript{24} and both the 1998 and 2010 guidances recommend PK studies be conducted in dialysis patients if there is the likelihood that an NCE will be prescribed for them.\textsuperscript{30} Studies to quantify the impact of RRT were only conducted for 21.6% of the 194 NCEs or 30.2% of the 139 that had a renal study done. High-fe NCEs were evaluated 44.2% of the time and low-fe NCEs 26% of the time, and dosage adjustments for dialysis patients were included in the APIs 84% of the time. Each study used a small number of dialyzers, often only 1, yet it was rare that the dialyzer model or details of the dialysis prescription were specified. This makes extrapolation of the data to patient care situations very tenuous because there are more than 125 different dialyzers marketed within the United States.\textsuperscript{25} Indeed, the KDIGO consensus panel recommended that \textit{in vitro} to \textit{in vivo} correlations be characterized to facilitate the extrapolation of the hemodialysis clearance data from one dialyzer to another.\textsuperscript{3} Because marked variability in the hemodialysis clearance of many drugs has been noted when dialyzers of different composition, size, and structure are used,\textsuperscript{26} the utility of a PK study of one dialyzer does little to assure clinicians that the dosage recommendations are optimal for all the patients in their care. Finally, although the hemodialyzers utilized in PK studies, especially those conducted during the last 5–10 years, were likely high permeability and designed for single use,\textsuperscript{25,27,28} up to 40% of dialysis treatments in clinical practice use reprocessed dialyzers.\textsuperscript{29} If reprocessing is being used in a dialysis facility, the clearance of some drugs maybe markedly affected and the value of the API dosage recommendations compromised.\textsuperscript{30}

The utility of the PK data and API dosage recommendations for critically ill patients with AKI have been questioned since the chronicity of renal injury appears to have differential effects on residual renal and nonrenal clearance of several drugs.\textsuperscript{31–33} In addition, only rarely have data been generated on the efficiency of the many CRRT variants as part of the NCE approval process. Indeed only 1 NCE, voriconazole oral, was evaluated to determine PK changes associated with the delivery of CRRT during the 12-year observation period.\textsuperscript{34} The KDIGO consensus group and others have called on regulatory agencies to mandate PK evaluations in AKI patients including those receiving CRRT therapy.\textsuperscript{19}

Despite increased conduction of renal studies by industry and improvements in API language, challenges remain. The recent data from Canada by Farag et al\textsuperscript{35} coupled with previous reports from several investigators\textsuperscript{36–39} suggest that the prescription of excessive doses of some drugs remains common in CKD patients, despite the increased availability
of quality dosing information in APIs during the last decade. A lack of awareness by clinicians of the patient’s impaired renal function status does not seem to be the key factor. Further investigation into barriers of appropriate medication use among renally impaired patients is required.

Conclusion

This analysis indicates that there have been significant improvements in the frequency with which quality renal studies have been done for NCEs during the last 10–15 years. The 1998 FDA renal regulatory guidance was thus an effective policy tool. The modifications to the FDA guidance proposed in 2010 affect only a few of the elements in the 1998 guidance, such as the optimal index of renal function for patient inclusion and the dependent variable in the regression determination of the influence of renal function on an NCEs’ PK, and the mandate to assess all drugs, even those that are minimally renally eliminated. These changes will generate valuable timely data on more NCEs and thereby give clinicians the opportunity to improve patient management and clinical outcomes.

Acknowledgments

We thank Gilbert J. Burckart, PharmD, FCCP, FCP, from the Office of Clinical Pharmacology, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland, for his guidance and assistance.

Funding

This study was not funded by any organization or commercial entity. All authors are responsible for the work described in this article. All authors were involved in at least 1 of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data, and drafting the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

Declaration of Conflicting Interests

The authors have no conflicting interest to report. These data were presented in part at the American Society of Nephrology Kidney Week 2012, November 2, 2012 San Diego, CA.

References


29. Denny G, Golper T. Does hemodialyzer reuse have a place in current ESRD care: “To be or not to be”? *Semin Dial.* 2014;27:256–258.


**Supporting Information**

Additional supporting information may be found in the online version of this article at the publisher’s web-site.