

An Integrated Approach for Assessing the Impact of Renal Impairment on Pharmacokinetics of Drugs in Development: Pivotal Role of PBPK Modelling

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Strategies for conducting renal impairment (RI) studies during clinical development of small molecules requires integration of the “totality of evidence” approach. Although it is acknowledged that physiologically-based pharmacokinetic (PBPK) modeling can provide valuable insights for clinical study design and dose optimization in kidney disease, the approach has yet to become established in assessment of RI during drug development and regulatory submissions. Emerging data support an expanded integration of a PBPK model-informed approach in regulatory guidances on RI.

REGULATORY GUIDANCE RELATING TO ASSESSMENT OF RI ON PHARMACOKINETICS OF DRUGS

The US Food and Drug Administration (FDA) 2010 draft guidance¹ and the European Medicines Agency (EMA) 2015 guideline² relating to evaluation of the pharmacokinetics (PKs) of drugs in patients with decreased renal function, indicate that the effect of RI should be investigated for most small molecule (SM) drugs intended for chronic use, irrespective of their elimination pathways. For drugs mainly eliminated by nonrenal routes, a

reduced design RI study in non-dialyzed end-stage renal disease (ESRD) or patients with severe RI may be carried out initially. Further investigation of other RI classes may be indicated, if relevant, based on the study results. Although the impact of RI on the PK of drugs mainly eliminated by renal pathways is well established, it is less obvious that the absorption, distribution, metabolism, and excretion of drugs may change as a consequence of the disease and its progression.³ These changes, which have been attributed to accumulated uremic toxins, should be evaluated using PK

principles and a “totality of evidence” approach to determine whether systemic exposure is likely to be altered in patients with RI.⁴ In addition to the glomerular filtration rate, changes in hepatic metabolism, transporter-mediated uptake and efflux, and protein binding of a drug need to be considered.³ These factors, which may affect both nonrenal and renal clearance routes, can be investigated using PBPK modeling. We recommend that high fidelity PBPK models based on quantitative understanding of *in vivo* human clearance routes (e.g., biliary, renal, metabolic),⁵ should be used as part of an integrated approach for assessing the impact of RI on drug PK in development. A high fidelity PBPK model is one that includes sufficient mechanistic resolution and quantitative representation of measured or definitively inferred drug and system parameters of relevance to the intended context(s) of use.

Application of PBPK models is highlighted in the 2020 FDA draft RI guidance, including early use of this approach to support an expanded inclusion of patients with RI in clinical studies, thereby increasing the experience with a specific, possibly adapted, dosing regimen in this population.⁶ We propose that the upcoming revised guidance⁶ provides information on further applications of PBPK simulations to support safe and efficacious drug treatment in RI populations. This would then fall in line with the EMA scientific guidelines on clinical pharmacology and PK,⁷ including the 2015 RI guideline,² where it was envisaged that PBPK modeling could be useful for prediction of the effects of RI, especially for complex scenarios involving pharmacogenetics and drug-drug interactions (DDIs), despite that at the time of publication experience was limited.

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QUANTITATIVE ASSESSMENT OF THE EFFECTS OF RENAL IMPAIRMENT USING PBPK MODELING

Typically, PBPK model development following best practice approaches involves the use of clinical data from single and multiple ascending dose studies to verify drug exposure, and DDI or mass balance studies combined with *in vitro* metabolism data to elucidate and verify the relative contributions of metabolic or other clearance mechanisms.⁵ This approach, followed by the International Consortium for Innovation and Quality in Pharmaceutical Development in their recent publication,³ led to the development of PBPK models for 25 compounds, which were then applied with confidence, to predict the effects of RI on drug exposure across 50 study arms; 64% of predictions were within 1.25-fold of observed data and 84% within 1.5-fold. The prediction accuracy decreased with increasing severity of RI; predicted area under the curve (AUC) ratios were within 1.25-fold and 1.5-fold of observed data in 87.5% and 100% of mild RI cases ($n = 8$), 71% and 100% of moderate RI cases ($n = 14$), and 57% and 71% of severe RI/ESRD cases ($n = 28$). The compounds were mainly eliminated by cytochrome P450 (CYP) enzymes (36% of compounds > 50% CYP3A4 metabolized) with varying contributions of biliary excretion (12% > 25% biliary excreted) and renal clearance (20% \geq 25% renally excreted). Key changes in physiological parameters reflecting the effects of RI, included reductions in CYP enzymes, an increase in albumin and a decrease in α -acid-glycoprotein levels.⁸ Thus, if a drug binds mainly to albumin, the increased unbound fraction in plasma often observed in patients with RI, can to some extent, cancel out the effects of the reduction in CYP activity on total drug exposures. This mainly affects highly bound drugs; 36% of the compounds in the dataset were > 95% bound. Overall, the observed effects of RI on the drugs were modest, with maximum observed mean AUC ratios (RI/control) being 1.7, 2.2, and 2.2 for the mild, moderate, and severe/ESRD impairments categories, respectively. The findings of the study lend weight to the fact that PBPK modeling can predict with reasonable accuracy the effects of RI on the PK of drugs, mainly metabolized by CYP enzymes.

PBPK modeling could be applied early in drug development to provide an indication of the impact of RI, and throughout development to inform on untested scenarios once clinical data in patients with moderate or severe RI are available to verify the model. Indeed, such an approach was used to evaluate the effect of RI on a combination of the antipsychotic olanzapine and opioid receptor antagonist samidorphan (OLZ/SAM) in development for the treatment of patients with schizophrenia or bipolar I disorder.⁸ Both OLZ and SAM are mainly cleared via CYP-mediated metabolism with renal clearance contributions of 10 and 20%, respectively. During clinical development, it was of interest to investigate the effect of RI on the PKs of both drugs, as kidney disease is a comorbidity in some patients requiring treatment with

antipsychotic medications. High fidelity PBPK models, developed initially for assessment of the DDI liability of OLZ/SAM, were used to predict the effects of RI on the single-dose (SD) exposure of both drugs; increases > 1.5-fold were indicated in patients with moderate and severe RI.⁸ Thereafter, an SD clinical study was conducted to assess the effects of severe RI on OLZ/SAM as well as to inform the PBPK model prior to prospective simulations of multiple doses in patients with varying degrees of RI. After integration of *ex vivo* unbound fraction values from the clinical study, the PBPK models predicted reductions of 38% and 54% in OLZ and SAM total clearance, respectively, and AUC ratios of 1.5-fold and 2.2-fold in subjects with severe RI relative to healthy controls, which were entirely consistent with observed data.⁸

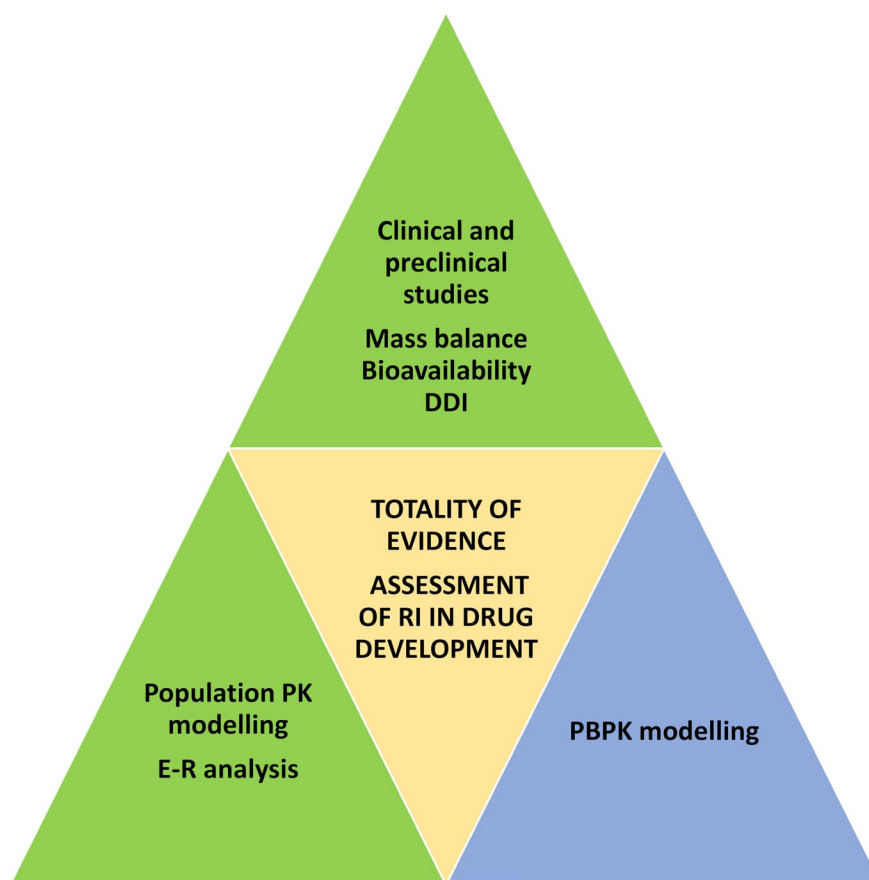


Figure 1 Integrated approach for assessment of renal impairment in drug development. A strategy to assess the need for carrying out RI studies during development using a “totality of evidence” approach would include review of the data from mass balance, absolute bioavailability, and DDI studies supported by model-based approaches such as population PK and PBPK modeling and exposure–response analysis put into context of the therapeutic window of the drug. DDI, drug–drug interaction; E-R, exposure response; PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic; RI, renal impairment.

AN INTEGRATED APPROACH FOR ASSESSING THE IMPACT OF RI ON PHARMACOKINETICS

SM oncology drugs are often administered at or close to the maximum tolerable dose and any increase in exposure due to RI could lead to safety issues. The findings of a survey of publicly available FDA review documents for 29 SM oncology drugs approved between 2010 and early 2015 indicated that the current FDA guidance (2010)¹ does not appear to provide clear strategic or decision pathways for RI studies, particularly for SM oncology drugs.⁴ The authors recommended a strategy to assess the need for carrying out RI studies during development using a “totality of evidence” approach.⁴ This typically includes review of data from mass balance, absolute bioavailability, and DDI studies supported by model-based approaches, such as population PK and exposure–response analysis put into context of the therapeutic window of the drug. For bosutinib, an oral Src/Abl tyrosine kinase inhibitor indicated for the treatment of patients with Philadelphia chromosome-positive chronic myelogenous leukemia, application of the totality of evidence approach appeared to provide justification for not carrying out a dedicated RI study based on data that were available for the 2012 new drug application submission.⁴ The main support was a population PK analysis, indicating a 30% reduced bosutinib clearance in patients with moderate RI, which lacked clinical significance. On review, the FDA found the population PK data limited and highly variable. The sponsor had already initiated an SD clinical study for bosutinib in patients with moderate and severe RI; plasma exposures increased by 1.4-fold and 1.6-fold, respectively.⁹ A PBPK model for bosutinib, developed to inform on clinical DDI studies, was included in the new drug application submission. However, it was only later that the PBPK model, after verification with the RI clinical data, was used to predict steady-state exposures of the drug in patients with moderate and severe RI.⁹ Today, the totality of evidence can be expanded to include PBPK simulations, which can provide valuable support for PK conclusions and, if used early during development, may lead to a higher

representation of patients with RI in a population PK dataset, and to a more conclusive analysis (Figure 1).

EVALUATION OF UNTESTED SCENARIOS AND EFFECTS OF MULTIPLE FACTORS INCLUDING DDIS

For drugs subject to both renal and hepatic elimination, the effect of drug interactions or pharmacogenetics (for example, eliglustat) may be more pronounced in patients with RI compared with healthy subjects, due to the added complication of a disease interaction. Both scenarios can be assessed using PBPK modeling. For bosutinib, accurate prediction of the observed CYP3A4-mediated DDIs in healthy subjects, as well as the increased exposure in

patients with mild and moderate RI and multiple dose exposure in patients with cancer, which typically forms part of the verification process of a PBPK model in drug development, would provide some confidence in prospective simulations of drug interactions at steady-state in patients with cancer with and without organ impairment.⁹

The antithrombotic rivaroxaban is eliminated by metabolism (60%) catalyzed by CYP3A and CYP2J2 and by renal excretion (40%) including P-glycoprotein/BCRP mediated secretion. During the FDA and EMA regulatory assessments, the risk of an enhanced interaction of moderate CYP3A inhibitors in patients with RI was raised. This was of particular concern

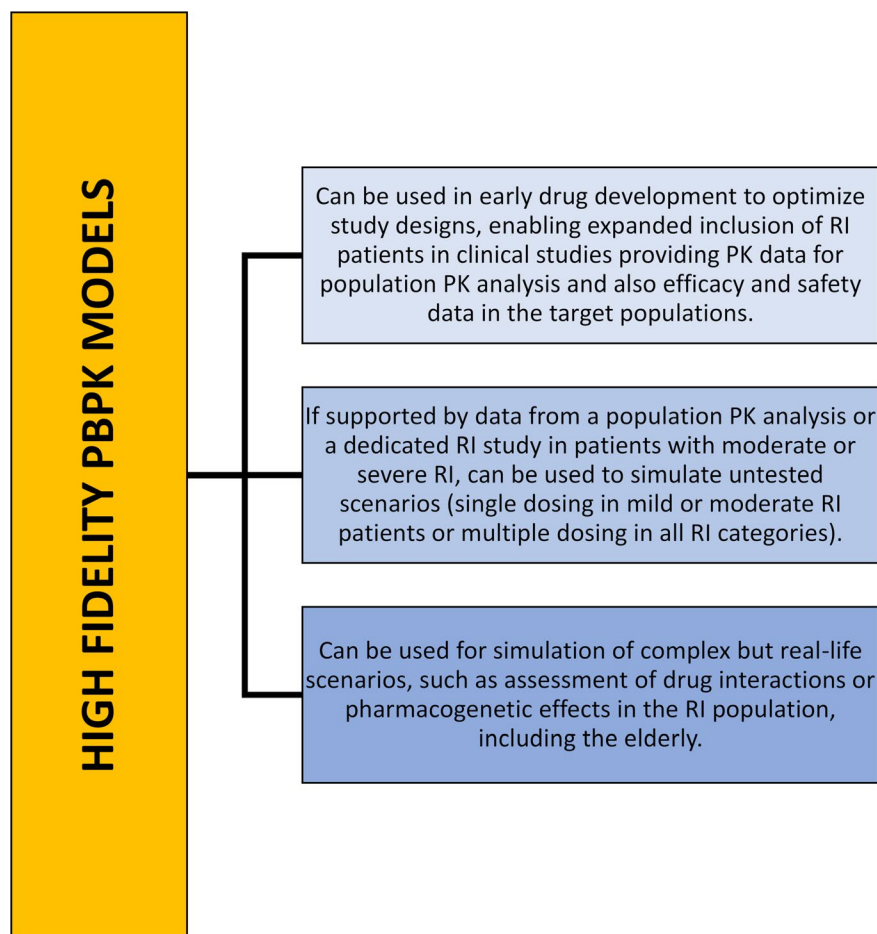


Figure 2 Applications of PBPK modeling for assessment of renal impairment during drug development. High fidelity PBPK models based on quantitative understanding of *in vivo* human clearance routes can be applied with confidence for various scenarios drug development and for regulatory decision making. A high fidelity PBPK model is one that includes sufficient mechanistic resolution and quantitative representation of measured or definitively inferred drug and system parameters of relevance to the intended context(s) of use. PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic; RI, renal impairment.

due to the safety consequences of increased rivaroxaban exposure, the elderly target population having a reduced renal function and the likely use of moderate CYP3A inhibitors in the population. The effects of RI and CYP3A inhibition had already been investigated individually *in vivo*. A PBPK approach was used to simulate the combined effect; it was concluded that although concomitant treatment with moderate CYP3A inhibitors was not of concern in patients with normal renal function, the interaction could be of safety concern in patients with mild to moderate RI. This information was reflected in the labeling of both regions and a postmarketing study was required by the FDA to further quantify the effects.¹⁰

CONCLUDING REMARKS

High fidelity PBPK models based on quantitative understanding of *in vivo* human clearance routes can provide accurate predictions of the effects of RI. These verified models can then be applied with confidence for various untested scenarios in drug development and for regulatory decision making (Figure 2). PBPK modeling should form part of an integrated approach for assessing the impact of RI on the PKs of drugs in development and current FDA guidance document should be updated to reflect this.

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CONFLICT OF INTEREST

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