The Readiness and Specific Paths of Using PBPK to Support Dosing Recommendation in Patients with Renal Impairment

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Outline

- **Model based approach to evaluate the effect of renal impairment (RI) on drug behavior**
- **Overview of predictive performance of PBPK for intended purposes**
- **Towards establishing predictive performance of PBPK for RI predictions**

Current labeling practice for RI

- **Silence**
  - No studies conducted, no recommendations
- **Data from dedicated studies**
  - *Gold standard, majority of recently approved drugs*
  - *Issues: Small "n", large variability → informativeness?*
- **Data from population PK (PopPK) studies**
  - *Getting popular*
  - *Issues: informativeness? Predictability for untested situations?*
- **Prospective predictions (e.g., PBPK)**
  - *Hardly used in the label*
  - *Issues: Predictive performance not established*

Model based approach

❑ PopPK models

FDA	EMA
"There may be a sufficient range of renal function" to allow the use of PopPK Considerations: • Sufficient number of subjects and a sufficient representation of a range of renal function • Measurement of unbound concentrations when appropriate • Measurement of potentially active metabolites as well as parent drug	"…if evaluation of effects of renal function on an investigational drug is indicated (see section 4), a phase I study should be conducted, if possible" Considerations: • Pre-planned, sufficient number of patients and a representative range of renal function • Results of the population analysis should not be extrapolated outside the studied range
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003122.pdf

❑ PBPK models (EMA only)

- Evolving field, foreseen to be useful particularly for drugs predominantly renally eliminated
- Need more knowledge on the effect of RI on metabolism, transport and protein binding or non-renally eliminated drugs

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Predictive methods

❑ Should be able to prospectively predict RI

- *Scenario 1. No RI information for drug of interest*
- *Scenario 2. Some RI information available (e.g. data in severe RI), other conditions not (clinically) tested*

❑ Require information on drug AND physiology of RI

- *Drug : absorption and disposition*
- *Physiology/disease: (quantitative) effect of RI on drug absorption/disposition pathways*

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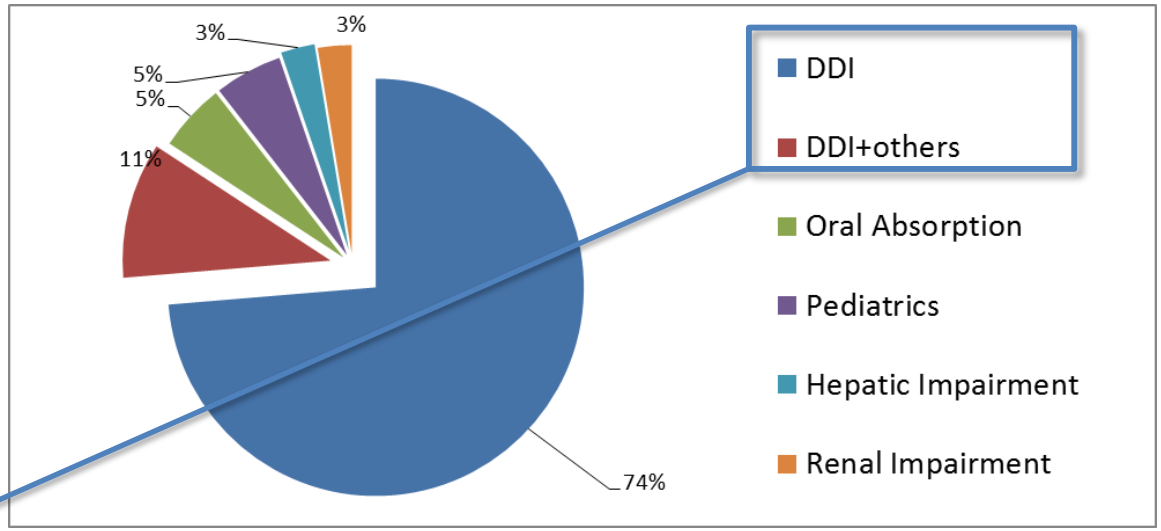
PBPK submissions to the FDA since 2004

As of June, 2014	As of Aug, 2016
n = 96 (60% DDI)	n = 217 (60% DDI)
Sinha, MHRA Workshop, 2014	*Zhao, EMA Workshop, 2016*

PBPK supporting dosing recommendations in US prescribing information (38 cases 2009-2016)



Greater confidence in predicting DDIs

DDIs: Drug-drug Interactions

Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

PBPK Model Describes the Effects of Comedication and Genetic Polymorphism on Systemic Exposure of Drugs That Undergo Multiple Clearance Pathways

MdLT Vieira[1], M-J Kim[1], S Apparaju[1], V Sinha[1], I Zineh[1], S-M Huang[1] and P Zhao[1]

Clin Pharmacol Ther, 2014

Predicting the Effect of Cytochrome P450 Inhibitors on Substrate Drugs: Analysis of Physiologically Based Pharmacokinetic Modeling Submissions to the US Food and Drug Administration

Christian Wagner · Yuzhuo Pan · Vicky Hsu · Joseph A. Grillo · Lei Zhang · Kellie S. Reynolds · Vikram Sinha · Ping Zhao

Clin Pharmacokinet 2015

Predicting the Effect of CYP3A Inducers on the Pharmacokinetics of Substrate Drugs Using Physiologically Based Pharmacokinetic (PBPK) Modeling: An Analysis of PBPK Submissions to the US FDA

Christian Wagner[1] · Yuzhuo Pan[2] · Vicky Hsu[1] · Vikram Sinha[1] · Ping Zhao[1]

Clin Pharmacokinet 2016

Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

$$R_{pred/obs} = \frac{Pred.Exposure\ Ratio}{Obs.Exposure\ Ratio}$$

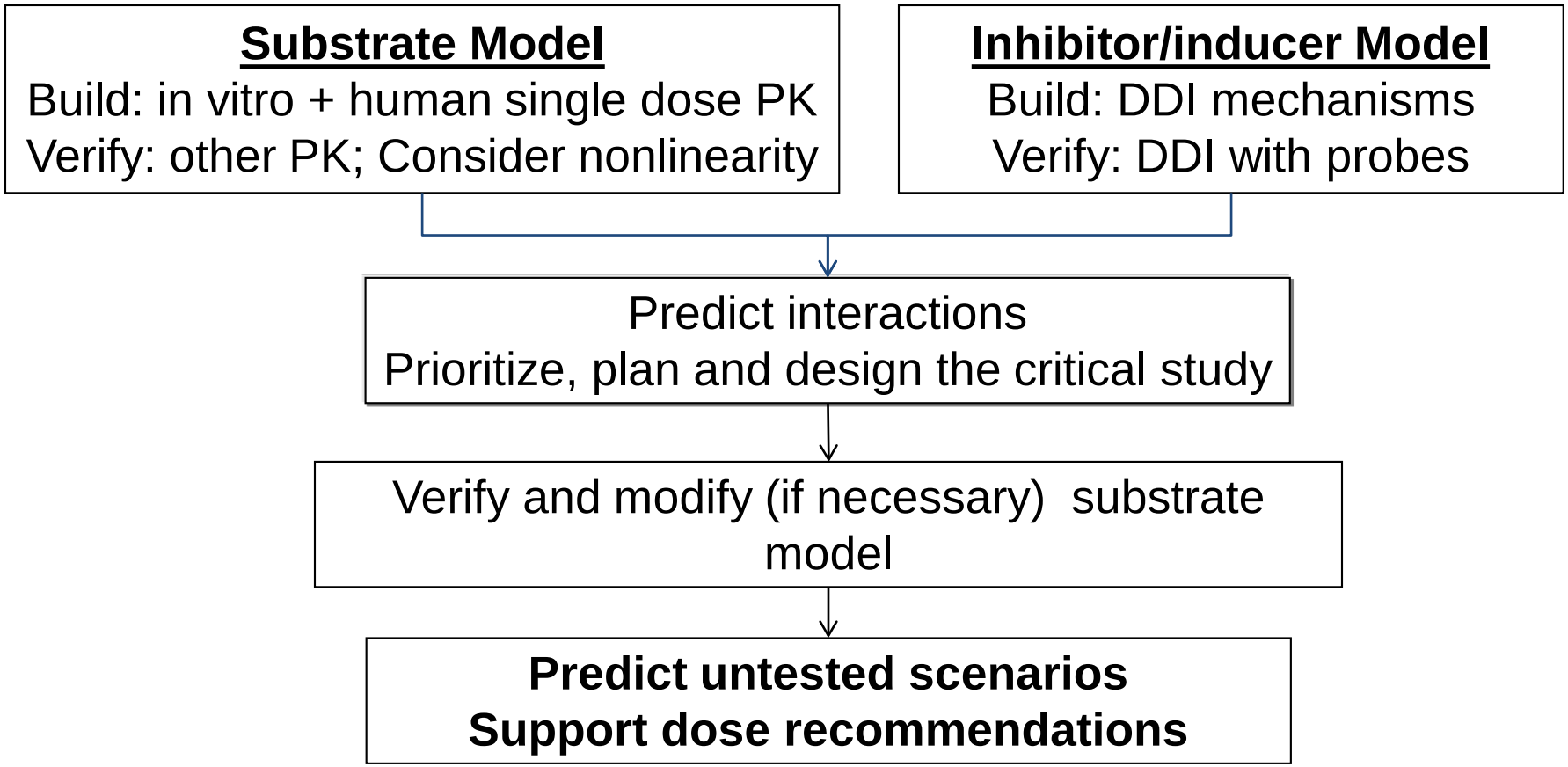
Exposure ratio: AUC or Cmax ratio (w/wo modulator)

	CYP Inhibition *(Vieira, 2014)*	**CYP Inhibition** *(Wagner/Pan, 2015)*	**CYP3A Induction** *(Wagner, 2016)*
Substrates evaluated	4	15	11
DDI cases to predict (external verification)	20	26	13
Organization	FDA	9 sponsors	6 sponsors
Substrate model predicts base PK (≤2-fold of observed clearance)	100%	87%	91%
$0.80 \le R_{pred/obs} \le 1.25$	72% AUC; 70% Cmax	81% AUC; 77% Cmax	77 % AUC; 83% Cmax
$0.50 \le R_{pred/obs} \le 2.00$	100%	100%	77% AUC; 92% Cmax
$R_{pred/obs} > 2.00$	0	0	23% AUC; 8% Cmax

Cut-off values are arbitrary

- *Under-prediction of induction using rifampicin model*
- *Rifampicin induces non-CYP3A pathways*

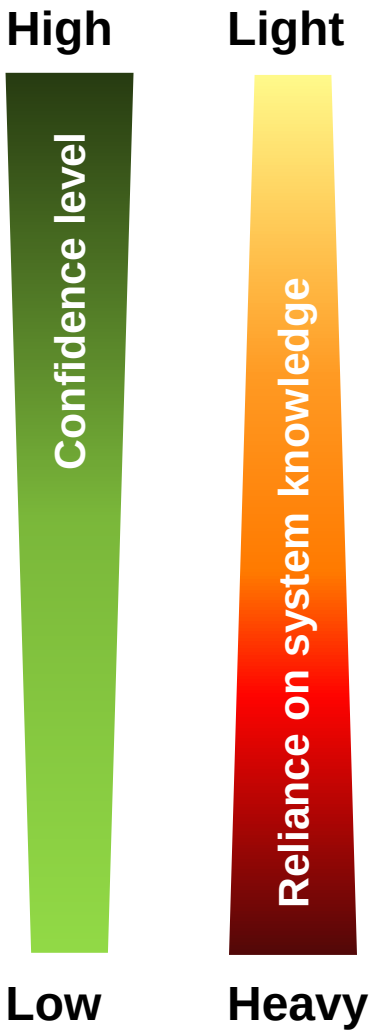
Established predictive performance allows the use of PBPK to predict the effect of CYP modulation



Wagner, CPT-PSP, 2015

PBPK applications: current status

	Applications	Status
Drug-drug Interactions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experience	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration*	



Wagner, CPT-PSP, 2015

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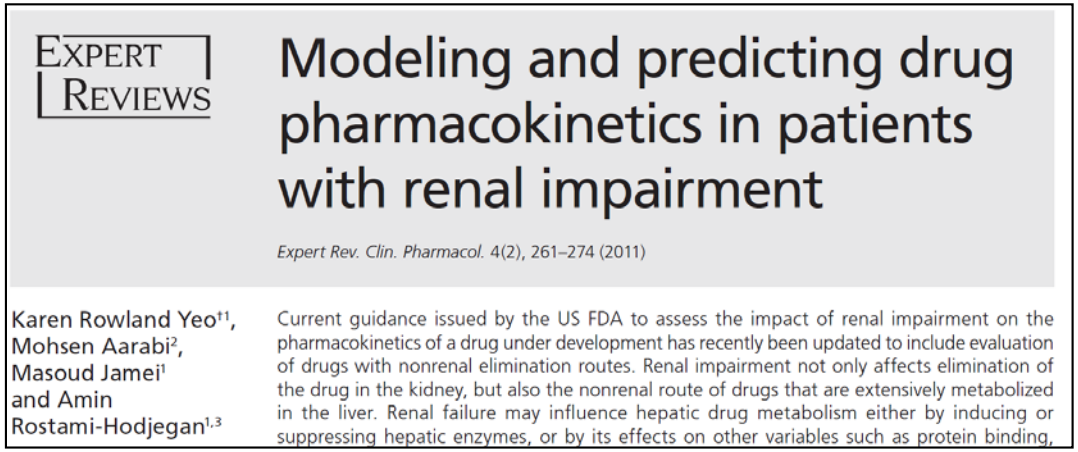
Implementing known changes during RI in PBPK models



EXPERT REVIEWS

Modeling and predicting drug pharmacokinetics in patients with renal impairment

Expert Rev. Clin. Pharmacol. 4(2), 261–274 (2011)

Karen Rowland Yeo[†1], Mohsen Aarabi[2], Masoud Jamei[1] and Amin Rostami-Hodjegan[1,3]

Current guidance issued by the US FDA to assess the impact of renal impairment on the pharmacokinetics of a drug under development has recently been updated to include evaluation of drugs with nonrenal elimination routes. Renal impairment not only affects elimination of the drug in the kidney, but also the nonrenal route of drugs that are extensively metabolized in the liver. Renal failure may influence hepatic drug metabolism either by inducing or suppressing hepatic enzymes, or by its effects on other variables such as protein binding,

Five-year view:

- Possible to extrapolate this (PBPK) approach to patients with RI
- Further research into the effect of RI on system parameters will “hopefully aid in the development of more robust models”

EMA RI guideline on PBPK (2014)

- Evolving field, foreseen to be useful particularly for drugs predominantly renally eliminated
- Need more knowledge on the effect of RI on metabolism, transport and protein binding or non-renally eliminated drugs

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003122.pdf

Changes relevant to renal clearance

Is "intact nephron hypothesis" sufficient?

- **Intact nephron hypothesis: proportional decrease in active secretion (CL_{sec}) and filtration (GFR) or**

$$\frac{CL_{sec\ RI}}{CL_{sec\ normal}} = \frac{GFR_{\ RI}}{GFR_{\ normal}}$$

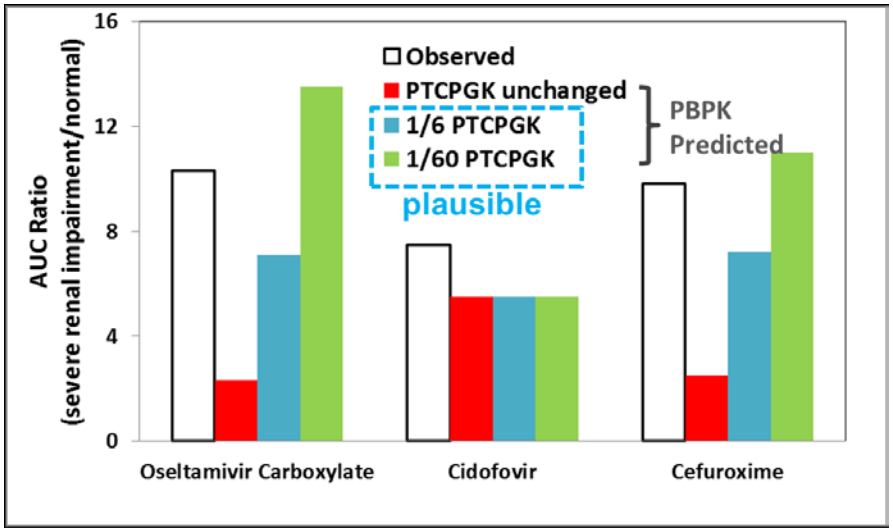
Changes relevant to renal clearance

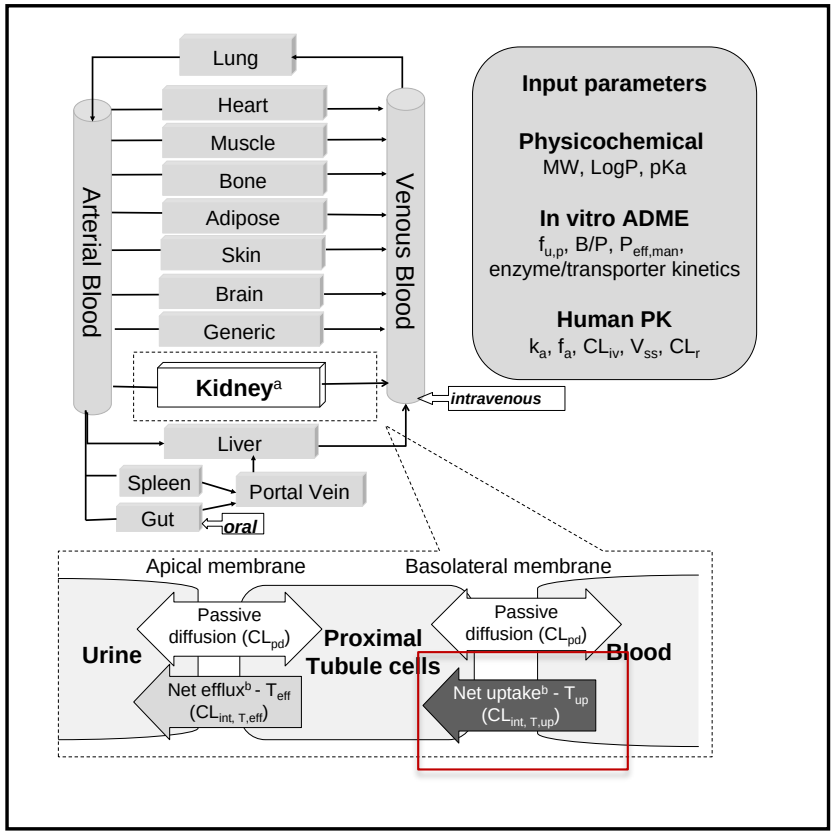
Clin Pharmacokinet
DOI 10.1007/s40262-013-0117-y

ORIGINAL RESEARCH ARTICLE

Towards Quantitation of the Effects of Renal Impairment and Probenecid Inhibition on Kidney Uptake and Efflux Transporters, Using Physiologically Based Pharmacokinetic Modelling and Simulations

Vicky Hsu · Manuela de L. T. Vieira · Ping Zhao · Lei Zhang · Jenny Huimin Zheng · Anna Nordmark · Eva Gil Berglund · Kathleen M. Giacomini · Shiew-Mei Huang





- **In the model, glomerular filtration rate (GFR) in severe RI subjects is ~1/6 of that in healthy subjects**
- **PTCPGK: (functional) proximal tubule cells per gram kidney, a system parameter, in severe RI needs to be 1/6-1/60 of that in healthy subjects**

Changes relevant to renal clearance

Is “intact nephron hypothesis” sufficient?

molecular pharmaceutics

Article

pubs.acs.org/molecularpharmaceutics

Identification and Quantitative Assessment of Uremic Solutes as Inhibitors of Renal Organic Anion Transporters, OAT1 and OAT3

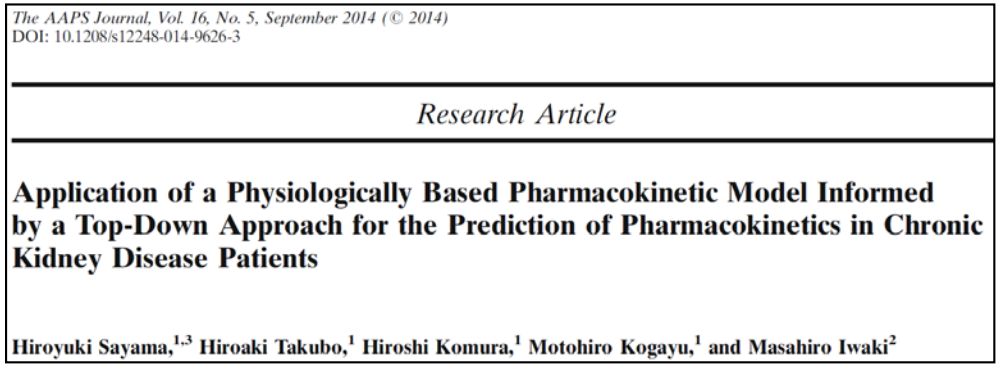
Chia-Hsiang Hsueh,[†,‡] Kenta Yoshida,[‡] Ping Zhao,[‡] Timothy W. Meyer,[§] Lei Zhang,[‡] Shiew-Mei Huang,[‡] and Kathleen M. Giacomini*[,†]

$$F_x = \left[\frac{CL_{sec\ RI}}{CL_{sec\ normal}}\right] \div \left[\frac{GFR_{RI}}{GFR_{normal}}\right]$$

=1: intact nephron hypothesis

<1 other factors (OAT substrates in severe RI)

Changes relevant to non-renal clearance



The AAPS Journal, Vol. 16, No. 5, September 2014 (© 2014)
DOI: 10.1208/s12248-014-9626-3

Research Article

Application of a Physiologically Based Pharmacokinetic Model Informed by a Top-Down Approach for the Prediction of Pharmacokinetics in Chronic Kidney Disease Patients

Hiroyuki Sayama,[1,3] Hiroaki Takubo,[1] Hiroshi Komura,[1] Motohiro Kogayu,[1] and Masahiro Iwaki[2]

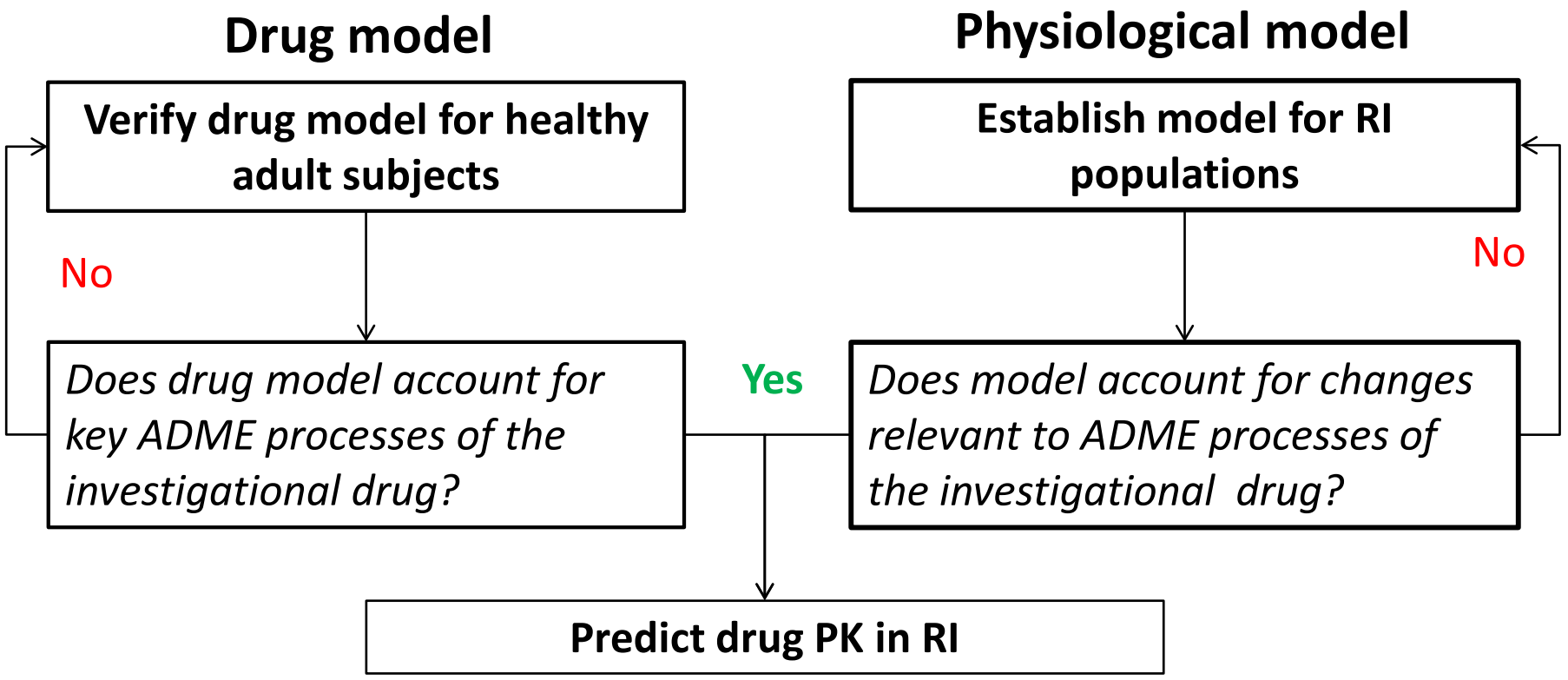
- Derive universal scaling factors (SFs) in CL_r, unbound hepatic intrinsic clearance ($CL_{u,int,H}$), and f_{up} in moderate and severe RI
- SFs were used in PBPK models to predict the effects on drug PK

Median SF values (% of control) for $CL_{u,int,H}$ are similar within category despite varying mechanisms of hepatic metabolism

	Moderate RI	Severe RI
All	68	62
CYP substrates	68	65
UGT substrates	67	59
Others	68	60

Modified from Table 2, Sayama et al, AAPS J, 2014

Proposed workflow to predict drug PK in a RI population using PBPK



Renally cleared drugs: Yee et al, manuscript submitted
Renally cleared OAT substrates: Hsueh et al, 2017 ASCPT Poster, manuscript submitted

Summary

- **Confidence of PBPK predictions varies, depending on predictive performance for intended purposes**
- **Establishing confidence in physiology (drug independent) model is crucial for effective use of PBPK to predict drug PK in RI**
- **Progress has been made towards prospective prediction of the effect of RI on PK of certain class of drugs using PBPK**

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U.S. FOOD & DRUG
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