A pharma industry PBPK perspective on the EMA qualification framework

To be presented at an EMA multi-stakeholder workshop on reporting and qualification of mechanistic models for regulatory assessment. 8 – 9 October 2025

A presentation in session 1: The qualification of mechanistic models through the EMA qualification framework and beyond

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A pharma industry PBPK perspective on the EMA qualification framework

Neil Parrott, F Hoffmann LaRoche, on behalf of EFPIA and a pharma industry PBPK expert team

A presentation in session 1: The qualification of mechanistic models through the EMA qualification framework and beyond

Introduction

EFPIA pharma industry PBPK expert team

Pradeep Sharma (AstraZeneca), Kunal Taskar (GSK); Neil Parrott (Roche); Ivana Tomic (Novartis); Caroline Sychterz (BMS); Theunis Goosen (Pfizer); Gareth Lewis (GSK), Priyanka Kulkarni (Takeda); Mary Choules (Astellas); Ryota Kikuchi (Abbvie); Maria Posada, Sonya Chapman and Ivelina Gueorguieva (Lilly); Jialin Mao (Genentech) and Loeckie de Zwart (Johnson & Johnson)

The presentation represents the collected experience and opinions of multiple pharmaceutical industry experts in PBPK modelling who have united efforts for the purpose of delivering optimal input to this meeting.

We received initial support and input from the IQ consortium (International Consortium for Innovation and Quality in Pharmaceutical Development)

Discussions were facilitated by the Simcyp Consortium Members Discussion Group

Final application and coordination was facilitated via EFPIA (European Federation of Pharmaceutical Industries and Associations)

We appreciate the opportunity to participate in this EMA multi-stakeholder workshop and thank the organizers for their work

Pharma industry perspective on PBPK qualification

Currently 3 routes are followed

1. within submissions - most common - resource intensive and repetitive - not very successful (Paul CPT 2025)

2. via CHMP Qualification Procedure - i.e. SimCYP. Limited to 1 case.

3. via publications by software platform independent cross industry consortia

Publications on PBPK qualification

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 685–695; doi:10.1002/psp4.12449

ARTICLE

Recommendations for the Design of Clinical Drug–Drug Interaction Studies With Itraconazole Using a Mechanistic Physiologically-Based Pharmacokinetic Model

Yuan Chen[1,*], Tamara D. Cabalu[2], Ernesto Callegari[3], Heidi Einolf[4], Lichuan Liu[5], Neil Parrott[6], Sheila Annie Peters[7], Edgar Schuck[8], Pradeep Sharma[9], Helen Tracey[10], Vijay V. Upreti[11], Ming Zheng[12], Andy Z.X. Zhu[13] and Stephen D. Hall[14]

42 citations

How this work supported DDI study waiver

Accurate simulation of the interaction of a substrate with itraconazole as a strong CYP3A inhibitor increases confidence in PBPK predictions for other inhibitors including weak and moderate inhibitors.
Multiple studies have been waived

- in vitro and clinical PK for ITZ and metabolites were collected from WG member companies
- in vitro data were generated to fill gaps
- ITZ PK data from 24 clinical studies
- 20 clinical DDI data sets for 7 substrates with various fm,CYP3A

- AUC ratios: 92% within guest criteria

Publications on PBPK qualification

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 110 NUMBER 2 | August 2021

WHITE PAPER

Physiologically-Based Pharmacokinetic Modeling in Renal and Hepatic Impairment Populations: A Pharmaceutical Industry Perspective

Tycho Heimbach[1,*,†], Yuan Chen[2], Jun Chen[3], Vaishali Dixit[4,†], Neil Parrott[5], Sheila Annie Peters[6], Italo Poggesi[7], Pradeep Sharma[8], Jan Snoeys[9], Mohamad Shebley[10], Guoying Tai[11], Susanna Tse[12], Vijay V. Upreti[13], Ying-Hong Wang[14,†], Alice Tsai[15], Binfeng Xia[16], Ming Zheng[17], Andy Z.X. Zhu[18] and Stephen Hall[19]

119 citations

95 citations

The AAPS Journal (2020) 22: 123
DOI: 10.1208/s12248-020-00508-2

Research Article

Theme: Use of PBPK Modeling to Inform Clinical Decisions: Current Status of Prediction of Drug-Food Interactions
Guest Editor: Filippos Kesisoglou

Use of Physiologically Based Pharmacokinetic (PBPK) Modeling for Predicting Drug-Food Interactions: an Industry Perspective

Arian Emami Riedmaier,[1,24] Kevin DeMent,[2] James Huckle,[3] Phil Bransford,[4] Cordula Stillhart,[5] Richard Lloyd,[6] Ravindra Alluri,[7] Sumit Basu,[8] Yuan Chen,[9] Varsha Dhamankar,[10,11] Stephanie Dodd,[12] Priyanka Kulkarni,[13] Andrés Olivares-Morales,[14] Chi-Chi Peng,[13,15] Xavier Pepin,[16] Xiaojun Ren,[17] Thuy Tran,[18] Christophe Tistaert,[19] Tycho Heimbach,[20] Filippos Kesisoglou,[21] Christian Wagner,[22] and Neil Parrott[23]

Very recent publications on PBPK qualification

WHITE PAPER

Current Practices, Gap Analysis, and Proposed Workflows for PBPK Modeling of Cytochrome P450 Induction: An Industry Perspective

Niresh Hariparsad[1,*], Diane Ramsden[2], Kunal Taskar[3], Justine Badée[4], Karthik Venkatakrishnan[5,6], Micaela B. Reddy[7], Tamara Cabalu[8], Dwaipayan Mukherjee[9], Jessica Rehmel[10], Jayaprakasam Bolleddula[5,6], Arian Emami Riedmaier[11], Chandra Prakash[12], Hugues Chanteux[13], Jialin Mao[14], Kenichi Umehara[15], Kushal Shah[16], Loeckie De Zwart[17], Martin Dowty[18], Masakatsu Kotsuma[19], Mengyao Li[20], Venkatesh Pilla Reddy[21], Dermot F. McGinnity[22] and Neil Parrott[15]

SYSTEMATIC REVIEW

Building Confidence in Physiologically Based Pharmacokinetic Modeling of CYP3A Induction Mediated by Rifampin: An Industry Perspective

Micaela B. Reddy[1,*,†], Tamara D. Cabalu[2,†], Loeckie de Zwart[3,†], Diane Ramsden[4], Martin E. Dowty[5], Kunal S. Taskar[6], Justine Badée[7], Jayaprakasam Bolleddula[8], Laurent Boulu[9], Qiang Fu[10], Masakatsu Kotsuma[11], Alix F. Leblanc[12], Gareth Lewis[6], Guiqing Liang[13], Neil Parrott[14], Venkatesh Pilla Reddy[15], Chandra Prakash[16], Kushal Shah[17], Kenichi Umehara[18], Dwaipayan Mukherjee[19], Jessica Rehmel[15] and Niresh Hariparsad[4,*]

CLINICAL PHARMACOLOGY & THERAPEUTICS October 2022 & Feb 2025

- Effort over ~5 years involving 25 PBPK modeling scientists representing 20 companies within IQ consortium
- Builds on prior groups collecting in vitro and clinical induction data
- Survey was submitted to 37 member companies to arrive at preliminary gap analysis and best practice workflows
- A major model qualification effort was then initiated to qualify rifampin mediated induction

Modeling plan and dataset definition

- PBPK models for 20 CYP3A well-characterized substrates with available rifampin DDI studies were collected
  - • fm,CYP3A4 : 0.086–1.0
  - • Fg : 0.11–1.0
  - • Fh : 0.09–0.96
- Substrates were binned into 2 tiers based on properties
  - Tier 1 : selective CYP3A substrates; not inhibitors or inducers of CYP3A; not OATP substrates
  - Tier 2 : compounds associated with greater complexity; OATP substrates; inhibitors and/or inducers of CYP3A
- Predictive performance subset
  - not used in Qgut or RIF model development; complete data package and followed the workflow including strong CYP3A4 inhibitor clinical study to validate Fg estimate

Model validation and verification

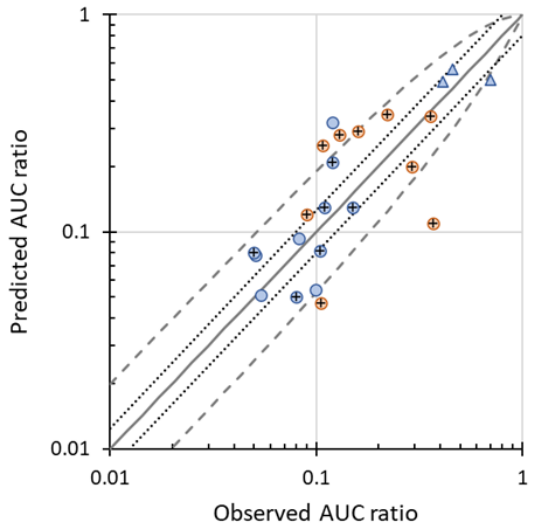
- Multiple-dose rifampicin model in Version 20
  - includes induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGT1A1 but no transporters but here CYP3A was the focus
  - IndC50 of 0.32 µM;IndMax of 16

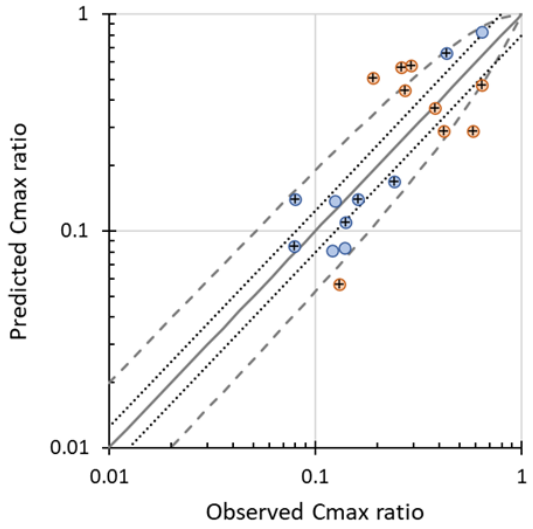
- Model validation workflow applied to all substrate models selected for analysis
  - human (ADME) study data required
  - single dose data; validation with strong inhibitor DDI

- Rifampin DDIs were simulated (10 IV, 34 PO)

- Assessed via forest plots for 90% PI's for GMRs for AUC and Cmax compared with observed GMRs and 90% CI's
- Geometric Mean-Fold Error (GMFE); Average Fold Error (AFE); Guest Criteria & Percent of Induction Captured

Results





Tier 1 = blue, well behaved
Tier 2 = orange, some challenges

PO = circles
IV = triangles

P-gp substrates marked with +

Most DDIs were well-predicted
Within Guest criteria
Tier 1: 91% AUCR and 100% CmaxR
Tier 2: 56% AUCR and 33% CmaxR

Accurate predictions when
i) no other inducible pathways not accounted for in the model
ii) Not P-gp substrates or P-gp substrates with high permeability

Case studies illustrate limitations

e.g.: **Tofacitinib** - Underprediction of rifampin DDI

◦ Metabolic Pathways: fm,CYP3A4 = 0.52 and fm,CYP2C19 = 0.17; renal elimination (fe = 0.31).

◦ DDI Observation: underprediction of the DDI

◦ Reasons for Discrepancy:
The tofacitinib model did not account for CYP2C19 induction. Incorporating CYP2C19 induction with Indmax = 16 did not significantly improve accuracy. A sensitivity analysis showed Indmax (20) did increase prediction accuracy.

◦ Learning: Highlights the need for a better understanding of induction mechanisms beyond just CYP3A other enzymes like CYP2C19

Credibility assessment

From ICH M15 DRAFT

Table 1: Guideline Overview: Sequence of MIDD in Relation to the Relevant Guideline Sections

Stages	Planning and Regulatory Interaction		Implementation, Reporting, and Submission		
Sequence of Activities	**Key Assessment Elements**	**Additional Considerations for Interaction with Regulator and to Inform Decision-Making**	**Model Evaluation**	**Model Analysis Reporting**	**Documentation for Regulatory Interactions and Submissions**
	• Question of Interest • Context of Use • Model Influence • Consequence of Wrong Decision • Model Risk • Model Impact	• Appropriateness of Proposed MIDD • Technical Criteria for model evaluation and model outcomes[1] These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation • Applicability assessment	• Model Analysis Report(s) (MAR)	• Regulatory documents, including + Outcome of MIDD Evidence Assessment + References to all relevant MAPs and MARs
Relevant Guideline Section	Section 2.1 and Appendix 1	Sections 2.2 and 4.1 and Appendix 1	Section 3	Section 4.2 and Appendix 2	Sections 2 and 4.3 and Appendix 1

Note: Terms used in this table are defined in relevant guideline sections.
[1] Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest.

Inform Decision-Making

Rifampicin qualification study explicitly followed the framework for credibility assessment as proposed in M15

Comparison of selection of datasets and best practice steps between Reddy et al. & EMA QO

- (1 CYP, 1 inducer, 20 substrates) vs (6 CYPs, 46 substrates, 28 inhibitors)
- Both highlight special considerations needed for transporter substrates (Reddy et al. puts OATP substrates in Tier 2 & considers Pgp in Tier 1 only if highly permeable)
- Both allow for parameter optimization using clinical data e.g. fm,CYP
- Similar criteria for substrate model in vitro input data (Physchem, solubility, permeability, PPB, BPR, in vitro metabolism and DDI data)
- Similar criteria for substrate model clinical data (SD, MD, mass balance, strong inhibitor study for fm)
- Similar matching for healthy volunteer populations and matching to clinical trials for simulations
- Similar approach with separate datasets for optimization & performance assessment

Comparison of metrics to EMA QO

Reddy et al.

Primary metric : GMR of AUCR and CMaxR

Statistical metrics

- 90% PI's for GMRs compared with observed GMRs and 90% Confidence Intervals, %of predictions within 2-fold, Guest et al. criteria). GMFE & AFE for precision and bias respectively
- Graphical Forest plots & Guest et al. plots

Looked at SD for substrate PK parameters

EMA QO

Primary metric : GMR of AUCR and CMaxR

Standard performance metrics (e.g. AAFE, AFE, within 1.5 fold, Guest et al.)

Bayesian meta-analysis

- Credible Intervals for the true GMRs used to represent uncertainty in predictions
- Plots of 90% CrI's for true GMR vs predicted GMR
- Bias as %difference between predicted & observed GMR

Stated that BSV of individual interaction ratios were under predicted. BSV prediction deemed out of scope.

Conclusions and Questions to be followed up

Multiple PBPK model qualifications for several contexts of use have been published

- They follow modeling best practices and similar performance metrics to the EMA QO
- These are increasingly following best practices (e.g. as outlined in ICH M15 DRAFT)
- Are the available published qualifications meeting the expectations of EMA?
  - If NO then what kind of additional considerations should be further included?

How to efficiently leverage cross-industry efforts to achieve a broader coverage of qualified PBPK applications in areas such as CYP induction?

Thank you

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