SimulationsPlus

Applying Mechanistic PBPK Modeling and Simulations to Support Regulatory Interactions

CSPS Canadian Society for Pharmaceutical Sciences
Société canadienne des sciences pharmaceutiques

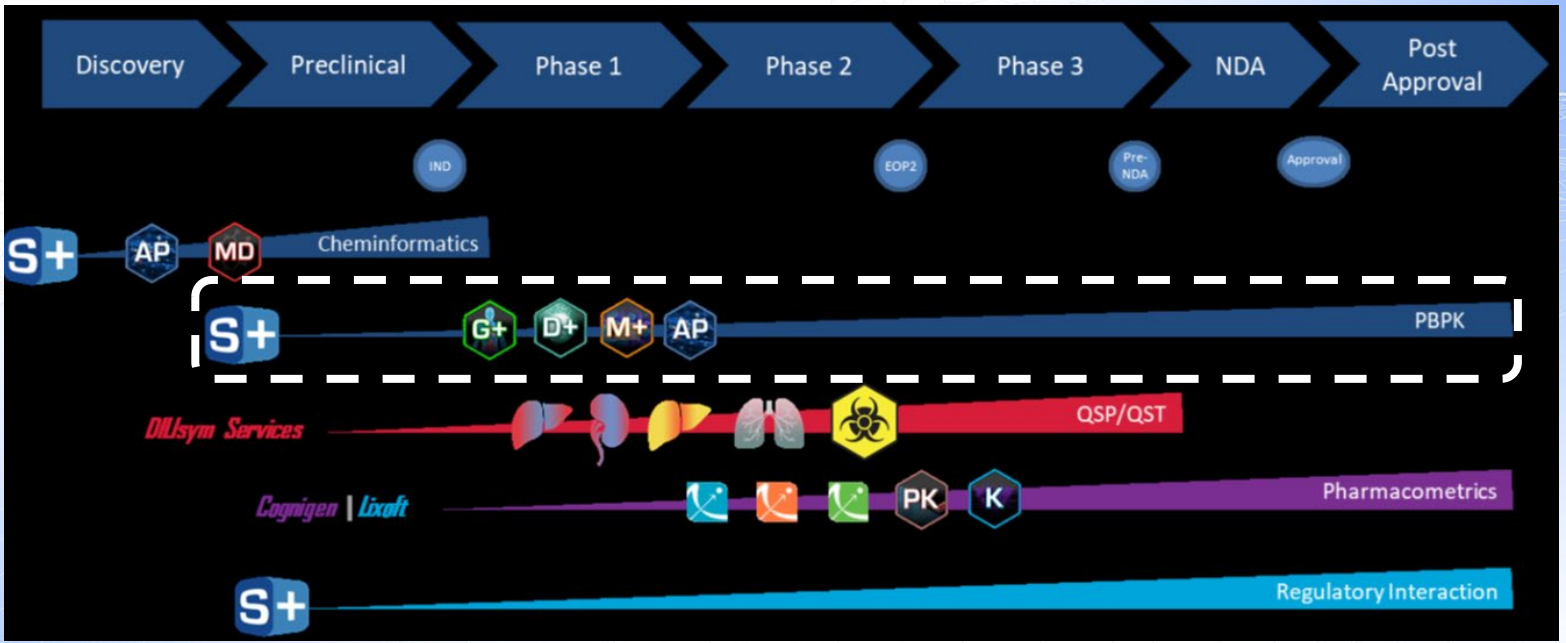
Toronto, May 26, 2023

Jasmina Novakovic
Simulations Plus Inc

Physiologically-Based Pharmacokinetic (PBPK) Modeling is a Tool/Component of Model-Informed Drug Development (MIDD)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6966181/pdf/PSP4-9-21.pdf

MIDD: Disciplines/Tools

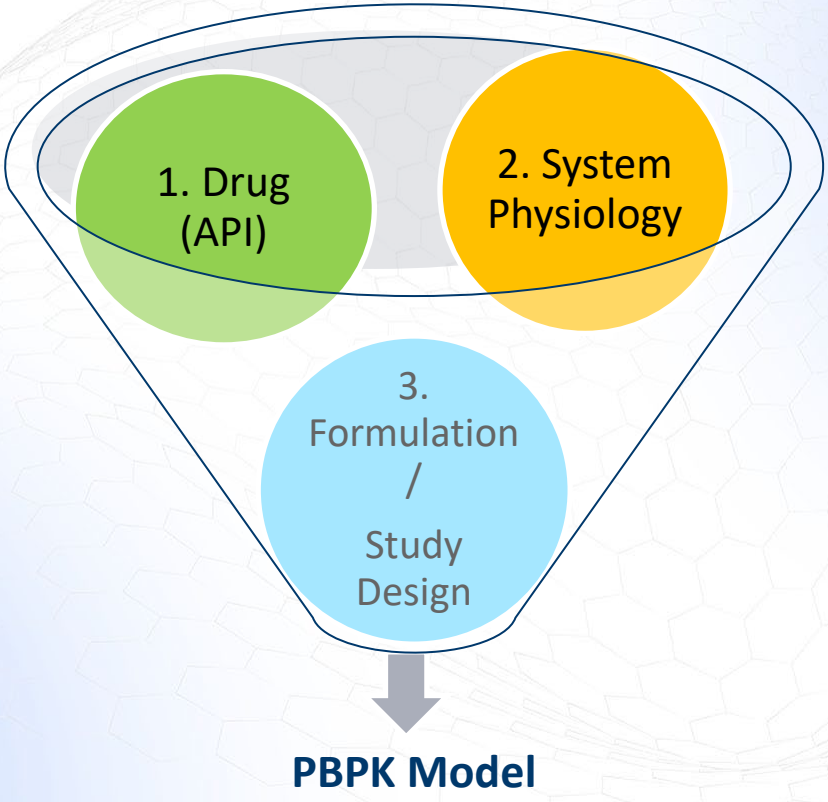


"**Model-informed drug development (MIDD) tools including physiologically based pharmacokinetic (PBPK) modeling can improve the mechanistic understanding of a drug's pharmacology and potentially translate into development efficiencies.**"

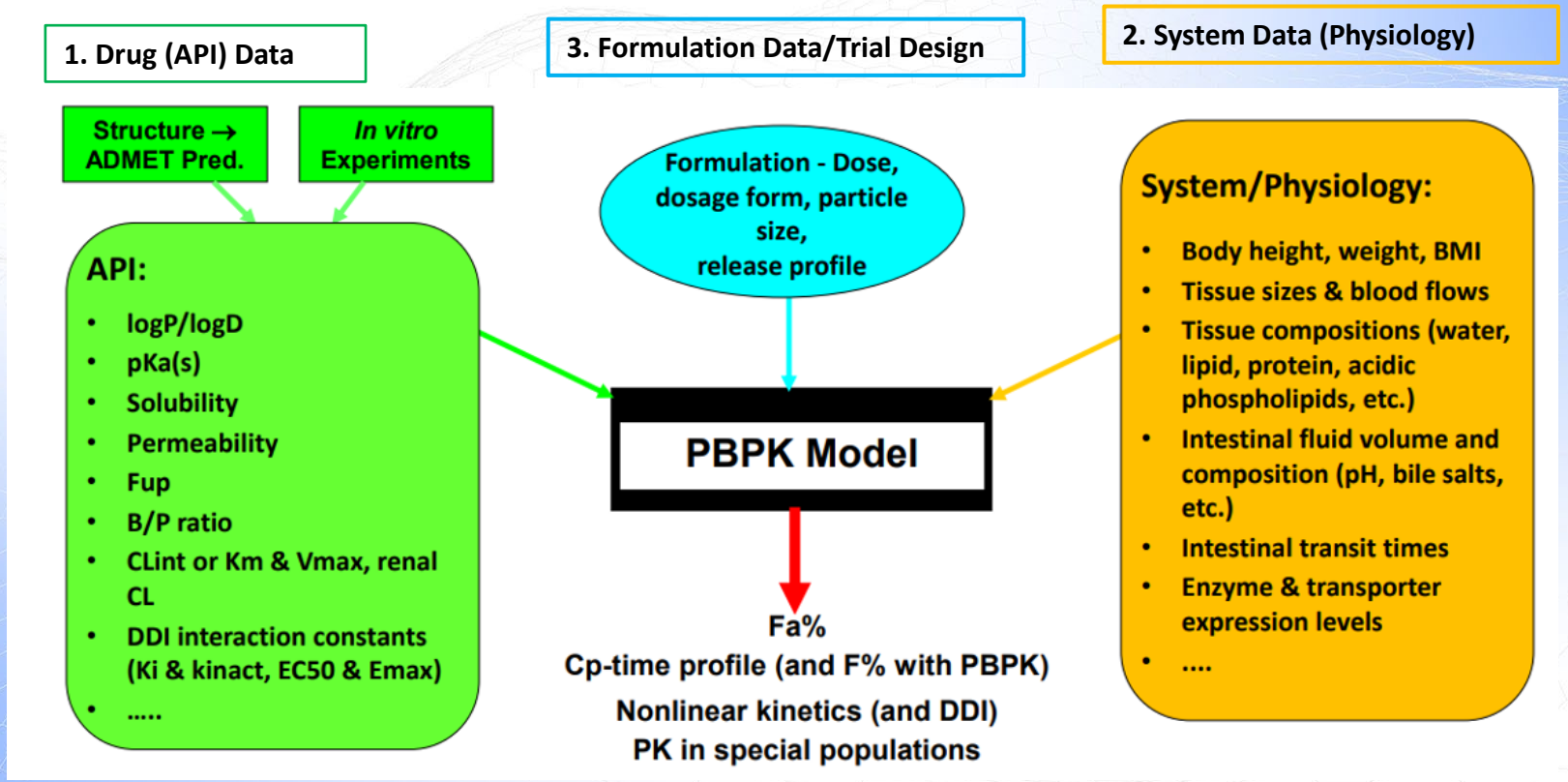
Kuemmel et al, CPT, 2020 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6966181/pdf/PSP4-9-21.pdf

AP = ADMET Predictor
MD = Medchem Designer
G+ = GastroPlus
D+ = DDD Plus
M+ = MembranePlus

PBPK Building Blocks

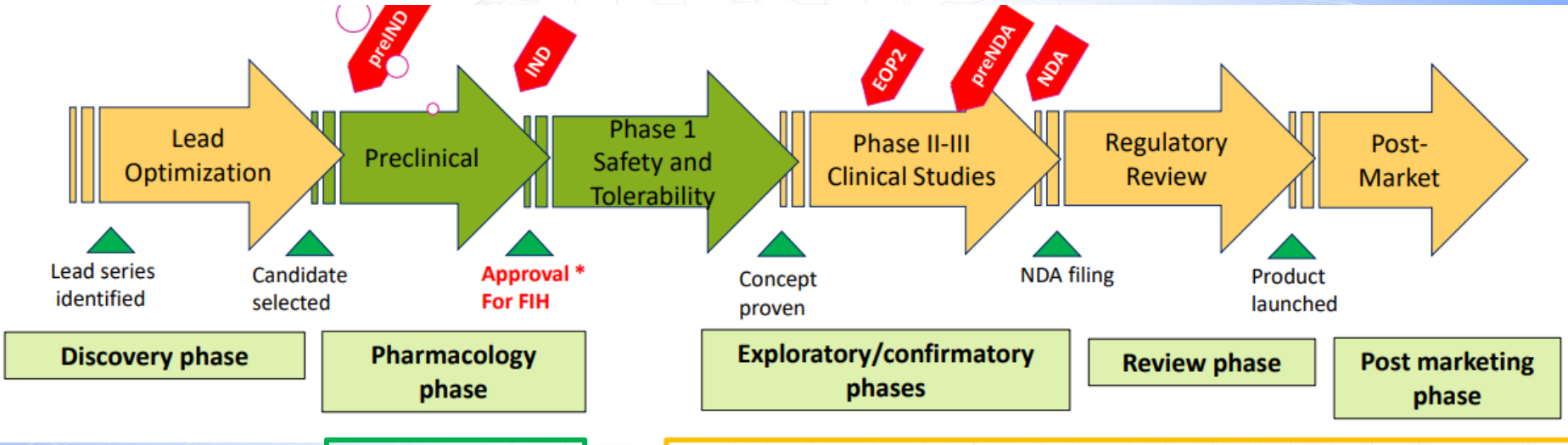


PBPK Building Blocks - Modeling Input



Lukacova V, AAPS 2018

Drug Development Pathway: Opportunities for PBPK



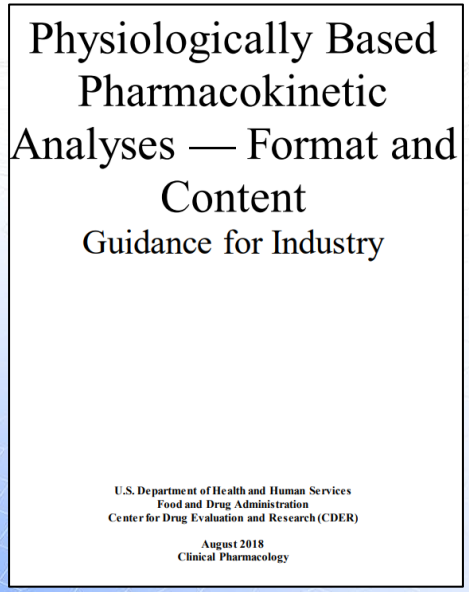
Regulatory authorities across the globe encourage utilization of PBPK during drug development pathway.

preIND = Pre-investigational new drug application; EOP2= End-of-phase 2 and pre-phase 3; preNDA =Pre-new drug application

Suarez Sharp, AAPS 2022

PBPK in Regulatory Guidance Documents

PBPK in FDA Guidance Documents



Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/physiologically-based-pharmacokinetic-analyses-format-and-content-guidance-industry

The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

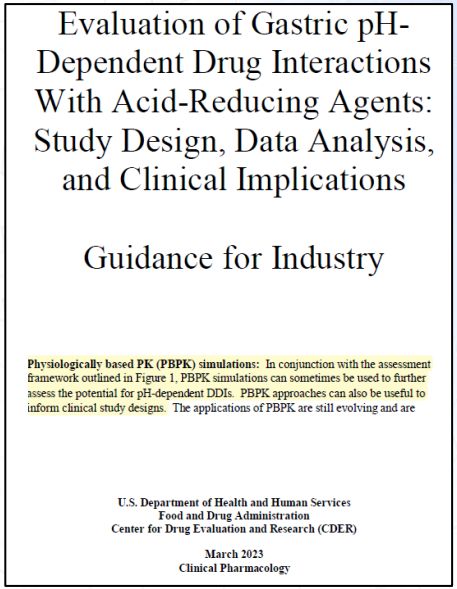
For questions regarding this draft document, contact Paul Seo at 301-796-4874.

PBBM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Pharmaceutical Quality/CMC

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product



Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

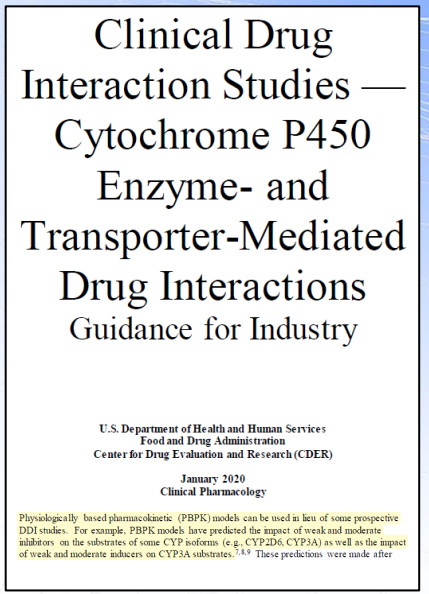
Guidance for Industry

Physiologically based PK (PBPK) simulations: In conjunction with the assessment framework outlined in Figure 1, PBPK simulations can sometimes be used to further assess the potential for pH-dependent DDIs. PBPK approaches can also be useful to inform clinical study designs. The applications of PBPK are still evolving and are

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2023
Clinical Pharmacology

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-gastric-ph-dependent-drug-interactions-acid-reducing-agents-study-design-data-analysis



Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

Guidance for Industry

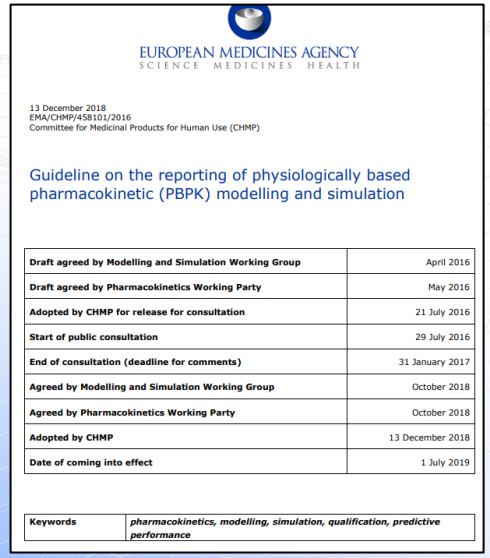
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2020
Clinical Pharmacology

Physiologically based pharmacokinetic (PBPK) models can be used in lieu of some prospective DDI studies. For example, PBPK models have predicted the impact of weak and moderate inhibitors on the substrates of some CYP isoforms (e.g., CYP2D6, CYP3A) as well as the impact of weak and moderate inducers on CYP3A substrates.[7,8,9] These predictions were made after

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions

PBPK in Guidance Documents from Other Jurisdictions



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

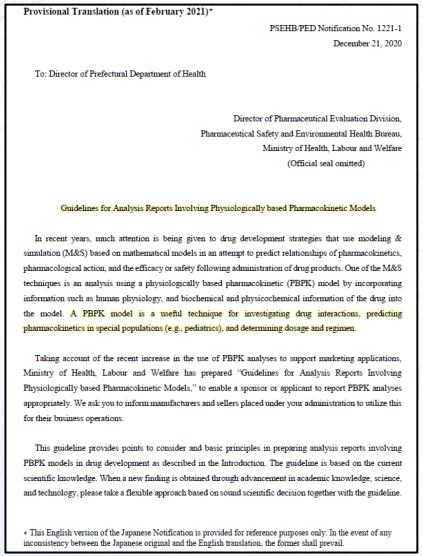
13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	***pharmacokinetics, modelling, simulation, qualification, predictive performance***

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf



Provisional Translation (as of February 2021)*

PSEHB/PED Notification No. 1221-1
December 21, 2020

To: Director of Prefectural Department of Health

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models

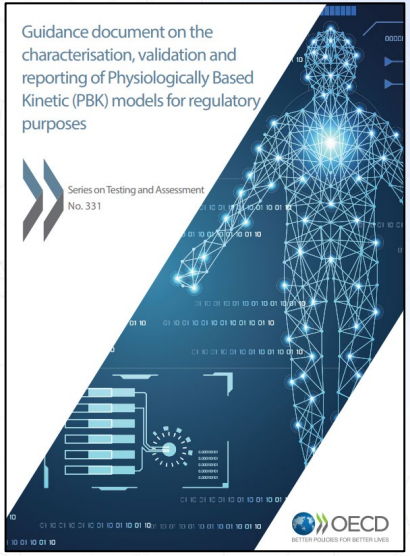
In recent years, much attention is being given to drug development strategies that use modeling & simulation (M&S) based on mathematical models in an attempt to predict relationships of pharmacokinetics, pharmacological action, and the efficacy or safety following administration of drug products. One of the M&S techniques is an analysis using a physiologically based pharmacokinetic (PBPK) model by incorporating information such as human physiology, and biochemical and physicochemical information of the drug into the model. A PBPK model is a useful technique for investigating drug interactions, predicting pharmacokinetics in special populations (e.g., pediatrics), and determining dosage and regimen.

Taking account of the recent increase in the use of PBPK analyses to support marketing applications, Ministry of Health, Labour and Welfare has prepared "Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models," to enable a sponsor or applicant to report PBPK analyses appropriately. We ask you to inform manufacturers and sellers placed under your administration to utilize this for their business operations.

This guideline provides points to consider and basic principles in preparing analysis reports involving PBPK models in drug development as described in the Introduction. The guideline is based on the current scientific knowledge. When a new finding is obtained through advancement in academic knowledge, science, and technology, please take a flexible approach based on sound scientific decision together with the guideline.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

000239317.pdf (pmda.go.jp)



https://www.oecd.org/chemicalsafety/risk-assessment/guidance-document-on-the-characterisation-validation-and-reporting-of-physiologically-based-kinetic-models-for-regulatory-purposes.pdf

The Organization for Economic Cooperation and Development

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

International scientific guideline: Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

EMA/CHMP/458101/2016 adopted by the Therapeutic Goods Administration (TGA)

https://www.tga.gov.au/resources/resource/international-scientific-guidelines/international-scientific-guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-and-simulation

PBPK & New Drugs Approval

PBPK in Regulatory Decision Making: New Drugs Approvals (FDA)

Application of PBPK Modeling and Simulation for Regulatory Decision Making and Its Impact on US Prescribing Information: An Update on the 2018-2019 Submissions to the US FDA's Office of Clinical Pharmacology

The Journal of Clinical Pharmacology 2020, 60(S1) S160–S178
Published 2020. This article is a U.S. Government work and is in the public domain in the USA
DOI: 10.1002/jcph.1767

Xinyuan Zhang, PhD, Yuching Yang, PhD, Manuela Grimstein, PhD, Jianghong Fan, PhD, Joseph A. Grillo, PharmD, Shiew-Mei Huang, PhD, Hao Zhu, PhD, and Yaning Wang, PhD

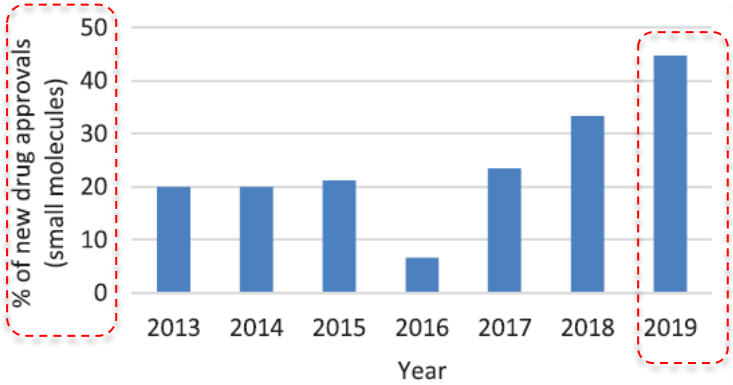


Figure 2. Percentage of new drug approvals containing physiologically based pharmacokinetics (2013-2019).

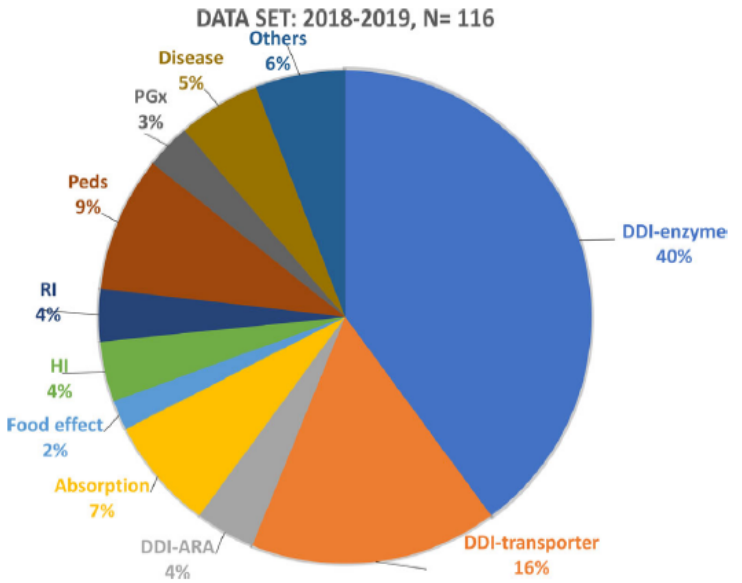


Figure 3. Distribution of physiologically based pharmacokinetic submissions by application areas (2018-2019). DDI-ARA, acid-reducing agent-mediated drug-drug interaction; DDI-enzyme, enzyme-mediated drug-drug interaction; DDI-transporter, transporter-mediated drug-drug interaction; HI, hepatic impairment; peds, pediatrics; PGx, pharmacogenomics; RI, renal impairment.

https://pubmed.ncbi.nlm.nih.gov/33205429/

DDI Case Study – Rivoceranib Example

Our Consulting Project, Presented at ASCPT2023

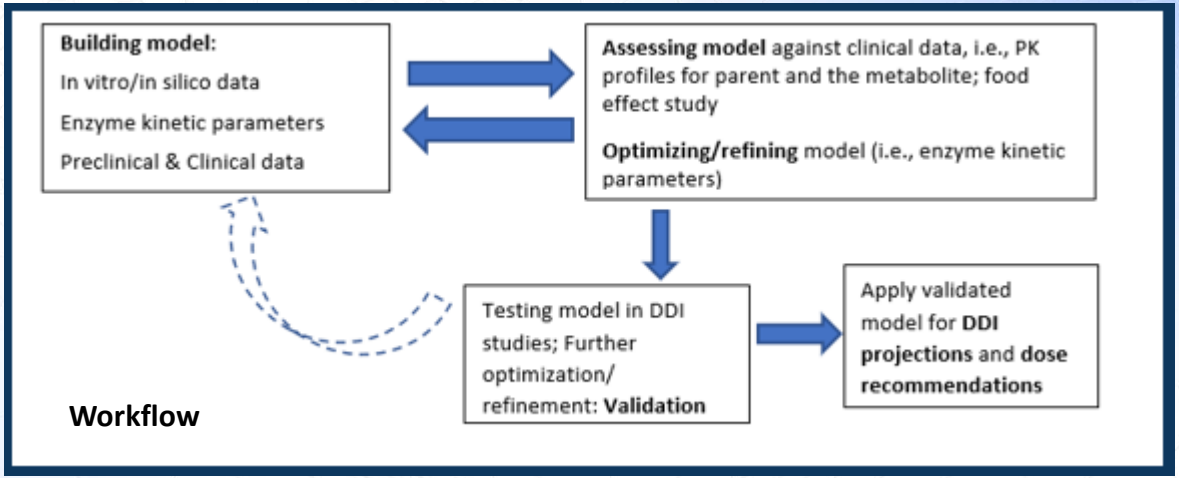
Physiologically Based Absorption and Pharmacokinetic Model for Rivoceranib and its Main Metabolite to Assess Potential CYP3A4-Mediated DDI Risk

Jasmina Novakovic[a], Grace Fraczkiewicz[a], Seong H Jang[b], Jeff Heckman[b], Bill Strickland[b], Mingyan Zhou[c], Nassim Djebli[c]

[a]Simulations Plus, Lancaster, CA; [b]Elevar Therapeutics, Salt Lake City, UT; [c]Luzsana Biotechnology, Princeton, NJ

Objective

A validated PBPK model is used *in lieu* of clinical studies to assess the risk of CYP3A4-mediated DDIs for an anticancer drug rivoceranib (victim) with weak/moderate CYP3A4 inhibitors (ranitidine/fluconazole), and with a moderate CYP3A4 inducer (efavirenz).



https://www.simulations-plus.com/wp-content/uploads/ASCPT2023_Poster_March_02_2023.FINAL_.pdf

PBPK Modeling Focused on Biopharmaceutics Applications (PBBM)

PBBM Regulatory Impact

The AAPS Journal (2021) 23: 31
DOI: 10.1208/s12248-021-00564-2

Commentary

Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs

Fang Wu,[1,2,9] Heta Shah,[3] Min Li,[1] Peng Duan,[3] Ping Zhao,[4,5] Sandra Suarez,[3] Kimberly Raines,[1] Yang Zhao,[1,6] Meng Wang,[1,7] Ho-pi Lin,[1] John Duan,[3] Lawrence Yu,[8] and Paul Seo[1,9]

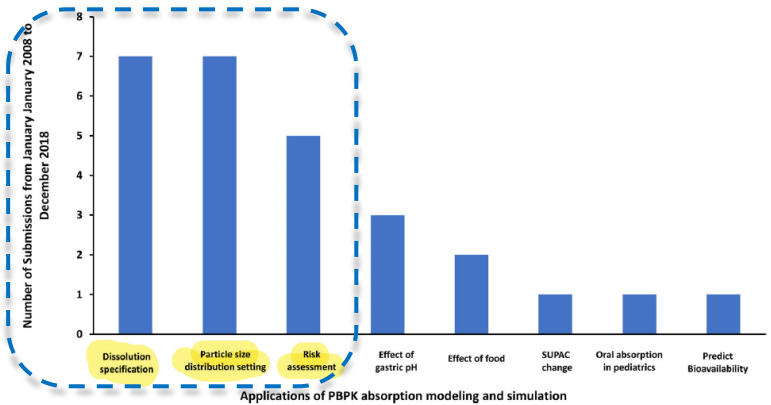


Fig. 2. Applications of PBPK absorption modeling and simulations in the new drug applications submissions*. Abbreviations: SUPAC, scale-up and post-approval changes. *Note that in some cases, the same model was used for multiple purposes, e.g., setting of both particle size specification and dissolution acceptance criteria

Pharmaceutical Research (2022) 39:1681–1700
https://doi.org/10.1007/s11095-022-03280-4

EXPERT REVIEW

The Use of Physiologically Based Pharmacokinetic Analyses—in Biopharmaceutics Applications -Regulatory and Industry Perspectives

Om Anand[1] · Xavier J. H. Pepin[2] · Vidula Kolhatkar[1] · Paul Seo[3]

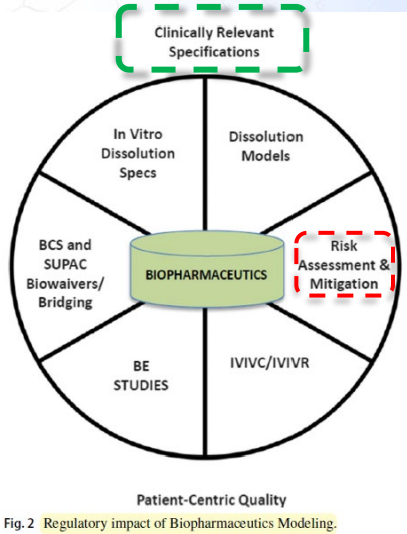


Fig. 2 Regulatory impact of Biopharmaceutics Modeling.

Patient centric quality standards (i.e., "safe space")

Improved life-cycle management

PBBM – Industrial Case Studies, Recent Publications

Journal of Pharmaceutical Sciences 000 (2021) 1–11

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Establishing the Bioequivalence Safe Space for Immediate-Release Oral Dosage Forms using Physiologically Based Biopharmaceutics Modeling (PBBM): Case Studies

Tycho Heimbach[a], Filippos Kesisoglou[a,*], Jasmina Novakovic[b], Christophe Tistaert[c], Martin Mueller-Zsigmondy[d], Sivacharan Kollipara[e], Tausif Ahmed[e], Amitava Mitra[f], Sandra Suarez-Sharp[g]

PHARMACOKINETICS, PHARMACODYNAMICS AND DRUG TRANSPORT AND METABOLISM | VOLUME 111, ISSUE 12, P3397-3410, DECEMBER 2022 Download Full Issue

Utility of Physiologically Based Biopharmaceutics Modeling (PBBM) in Regulatory Perspective: Application to Supersede f2, Enabling Biowaivers & Creation of Dissolution Safe Space

Adithya Karthik Bhattiprolu • Sivacharan Kollipara • Tausif Ahmed • Rajkumar Boddu • Siddharth Chachad

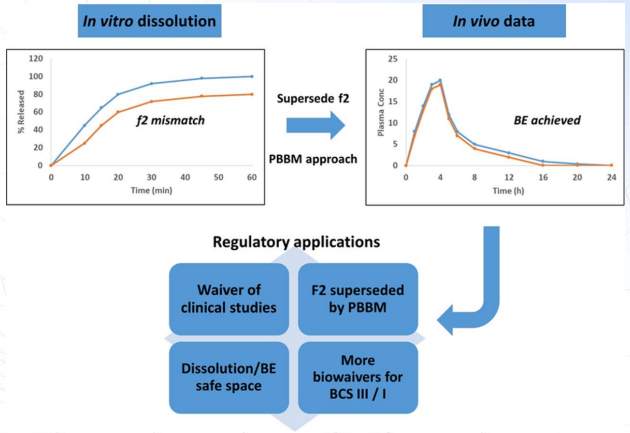
Published: September 09, 2022 • DOI: https://doi.org/10.1016/j.xphs.2022.09.003 • Check for updates

Pharmaceutical Research
https://doi.org/10.1007/s11095-022-03319-6

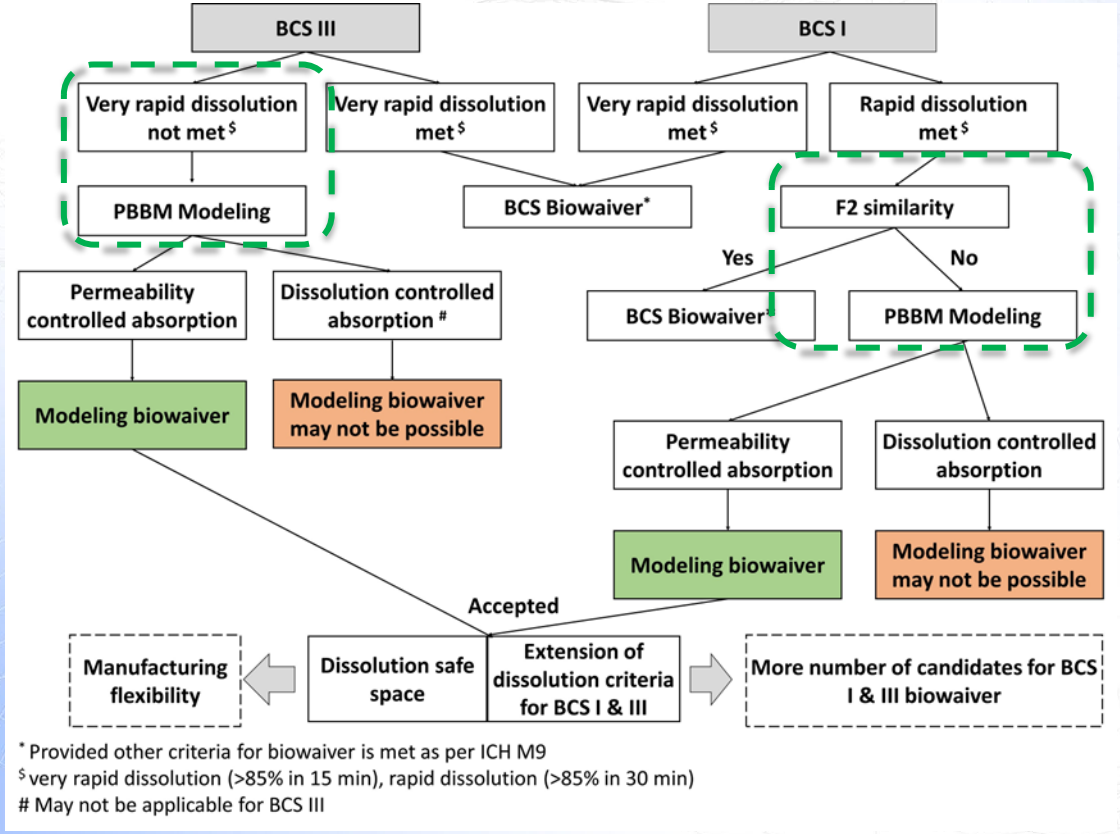
EXPERT REVIEW

Physiologically Based Pharmacokinetics Modeling in Biopharmaceutics: Case Studies for Establishing the Bioequivalence Safe Space for Innovator and Generic Drugs

Di Wu[1] · Maitri Sanghavi[2] · Sivacharan Kollipara[3] · Tausif Ahmed[3] · Anuj K Saini[2] · Tycho Heimbach[1]



Biowaiver Strategies for BCS III and BCS I Drugs: Decision Tree



Adithya Karthik Bhattiprolu , Sivacharan Kollipara , Tausif Ahmed , Rajkumar Boddu , Siddharth Chachad , Utility of Physiologically Based Biopharmaeutics Modeling (PBBM) in Regulatory Approval: Application to Supersede f2, Enabling Biowaivers & Creation of Dissolution Safe Space, *Journal of Pharmaceutical Sciences* (2022)

Ahmed T. (2023) MIDD+ Virtual Conference

Summary of PBPK/PBBM Applications with Regulatory Impact

EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 27 (2006) 91–99

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/ejps

A strategy for preclinical formulation development using GastroPlus™ as pharmacokinetic simulation tool and a statistical screening design applied to a dog study

Martin Kuentz, Sonja Nick, Neil Parrott, Dieter Röthlisberger*

F. Hoffmann-La Roche Ltd., Pharmaceutical and Analytical R&D, Bldg./Lab. 072/338, Grenzacherstr., CH-4070 Basel, Switzerland

Clinical Pharmacokinetics (2019) 58:727–746
https://doi.org/10.1007/s40262-019-00741-9

REVIEW ARTICLE

Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies

Neil A. Miller[1] · Micaela B. Reddy[2] · Aki T. Heikkinen[3] · Viera Lukacova[4] · Neil Parrott[5]

Prediction of pH-Dependent Drug-Drug Interactions for Basic Drugs using Physiologically based Biopharmaceutics Modeling: Industry Case Studies

Amitava Mitra, Neil Parrott, Neil Miller, Richard Lloyd, Christophe Tistaert, Tycho Heimbach, Yan Ji, Filippos Kesisoglou

PII: S0022-3549(19)30797-X

DOI: https://doi.org/10.1016/j.xphs.2019.11.017

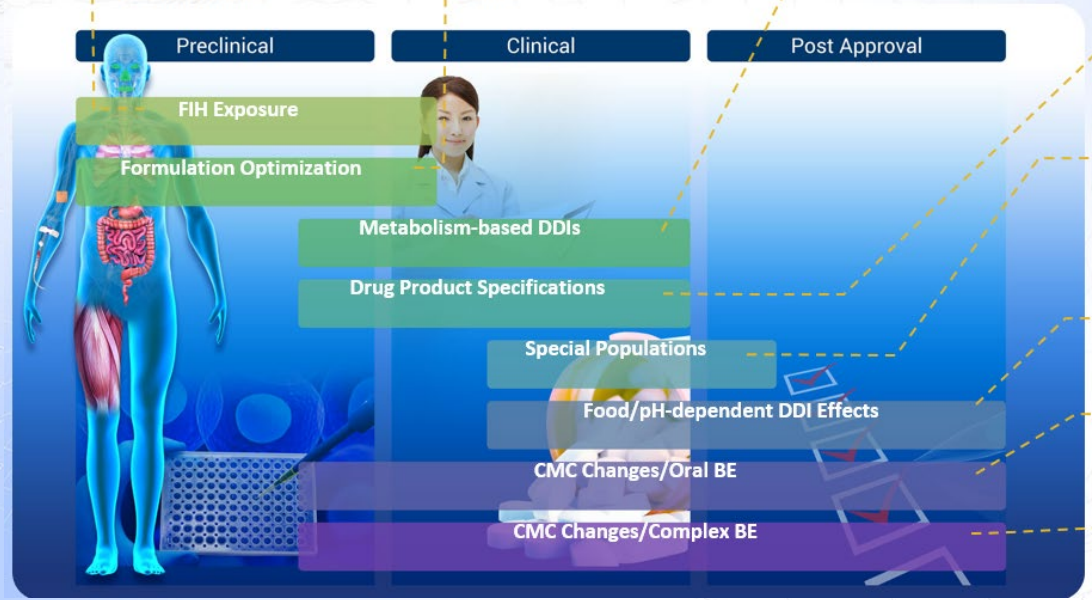
Reference: XPHS 1813

To appear in: *Journal of Pharmaceutical Sciences*

FIH dose selection and clinical development plans based on preclinical data

Support for optimal formulation selection based on preclinical data

Predictions of DDI liability; DDI study design support and biowaiver plans



Development of biopredictive dissolution methods and drug product specifications

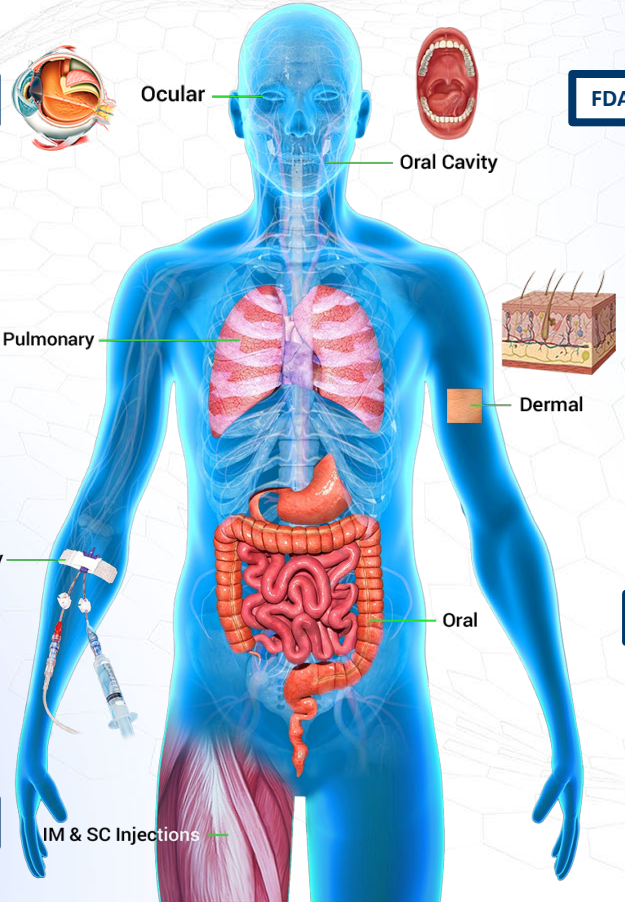
Simulations to support dose adjustments in special populations and related product labelling

Design studies and biowaiver plans

Design of BE studies and biowaiver plans for oral route of administration

Design of BE studies and biowaiver plan for complex products

PBBM Beyond Oral Administration: Collaborative Projects with FDA



FDA: Ocular PBBM extensions

FDA: Oral cavity PBBM extensions

FDA: Pulmonary PBBM extensions

FDA: Dermal PBBM extensions

FDA: Oral absorption PBBM extensions

FDA: Long-acting injection PBBM extensions

Courtesy of John DiBella

Acknowledgments

Thanks to Simulations Plus team - John, Viera, Grace, Sandra, and Xavier, for their input

Thanks to our client Elevar/Hengrui/Luzserna for the opportunity to support their biowaiver for clinical DDI studies and especially for being open to present the results in public domain