Physiology Based Pharmacokinetic Absorption Modeling in Generic Drug Product Development and Regulatory Decisions- Opportunities and Challenges

GastroPlus User Group webinar

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Disclosure Statement

The views expressed in this talk represent my personal opinions and do not necessarily represent the views of any organizations.

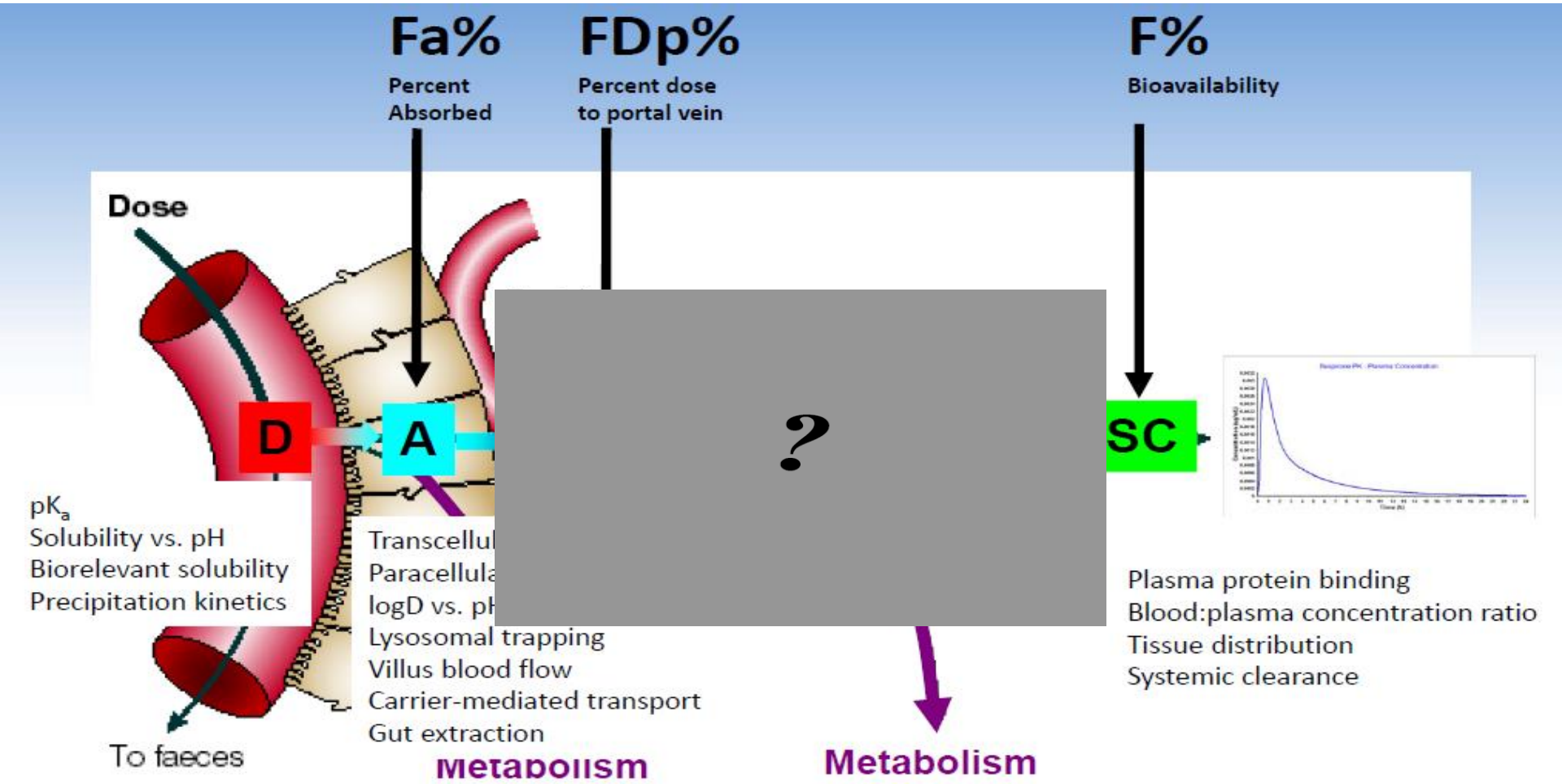
Abstract

Physiology based pharmacokinetic (PBPK) modeling is widely used within the pharmaceutical industry to predict oral drug absorption. The potential utility of PBPK absorption modeling in the regulatory setting has been highlighted by both industries and regulators. A recent survey of the pharmaceutical industry highlighted that in silico PBPK absorption modeling is widely used during development to address a variety of biopharmaceutics issues. Application of PBPK modeling to support clinically relevant specifications has been encouraged by various regulatory agencies. A sequential process of implementing PBPK modelling and simulation at various steps of generic drug product development is discussed. Various quintessential points are explained with relevant examples, and how PBPK modeling can accelerate the drug development process is highlighted. Further, challenges and ‘keep in mind’ points are discussed with regulatory filing perspectives.

Outline of the presentation:

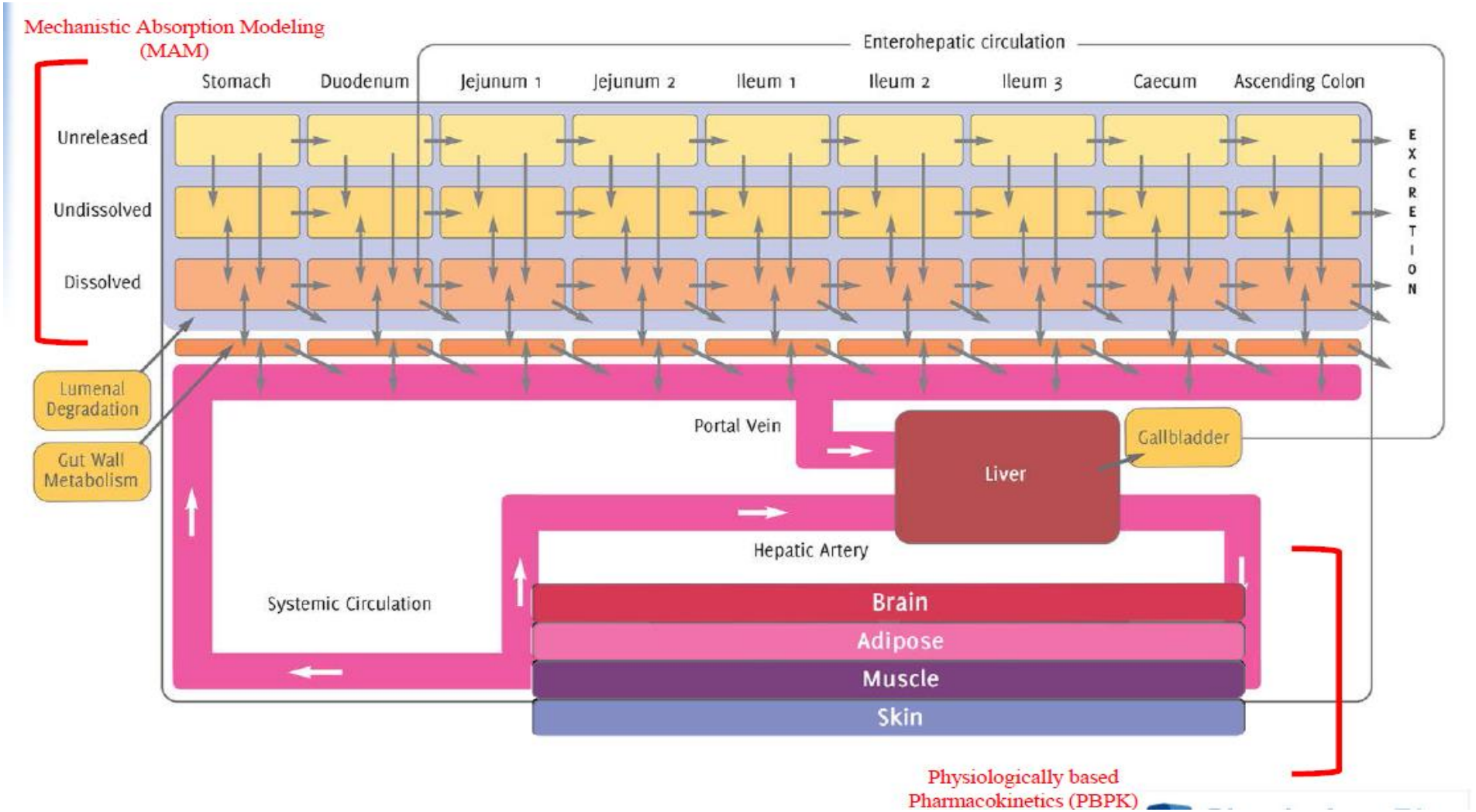
- Introduction
- Generic drug product development
- Application of modeling & simulation
- Regulatory impact of PBPK
- Simulation methodology & case studies
- Challenges & summary

Introduction: Mechanistic vs Conventional deconvolution

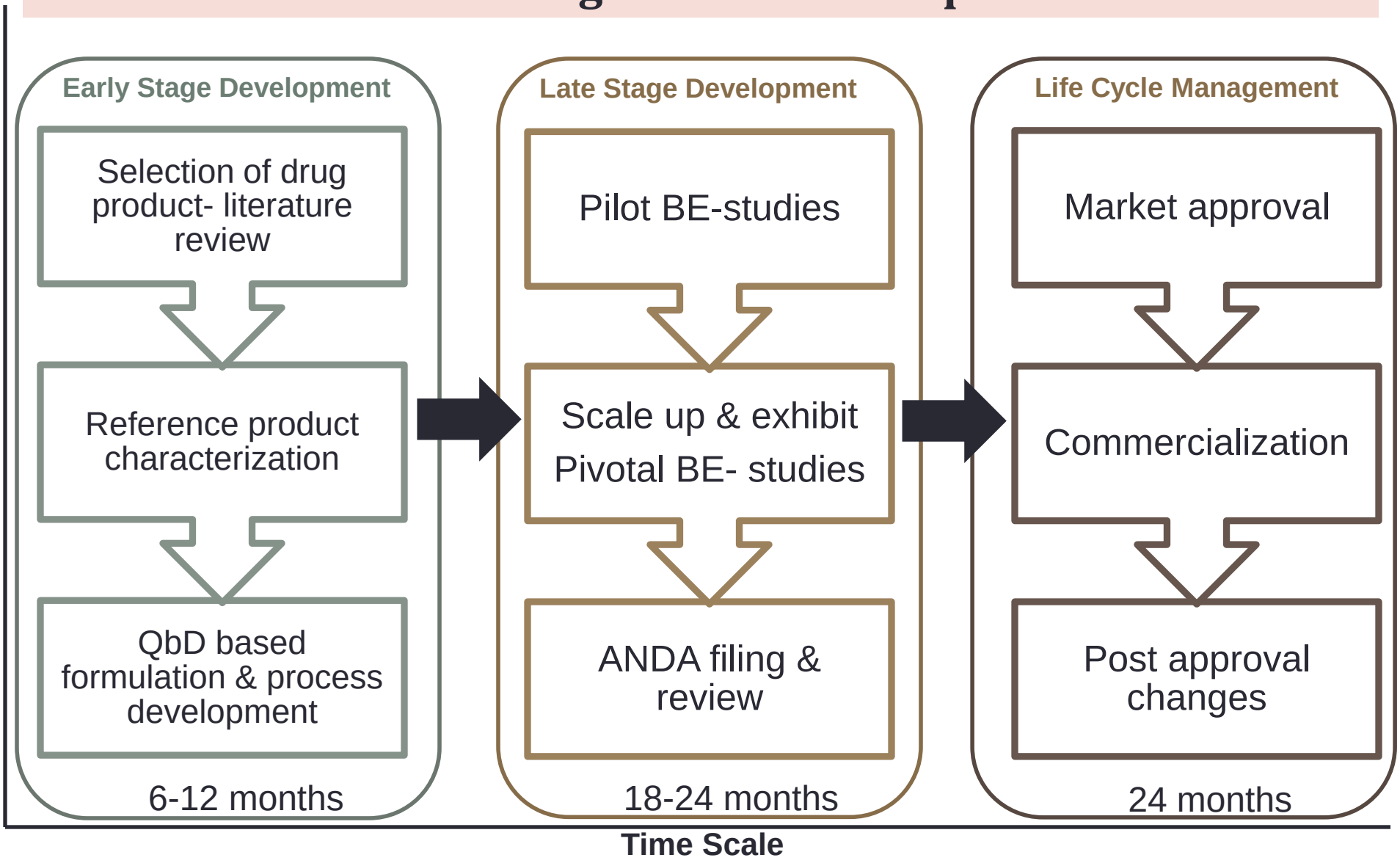


*Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

ACAT [Advanced Compartmental Absorption & Transit] Model



Generic Drug Product Development



Applications of PBPK in drug product development

Early and late development phase – Reduce trial & error

For formulation optimization

Understand the mechanisms that affect the absorption

Dissolution method and acceptance criteria:

Clinically relevant limits for CMAs and CPPs

Food effect assessment

Biowaiver

Post approval changes

To justify post approval CMC changes

To justify manufacturing site transfer

Regulatory impact of PBPK- USFDA- 2016

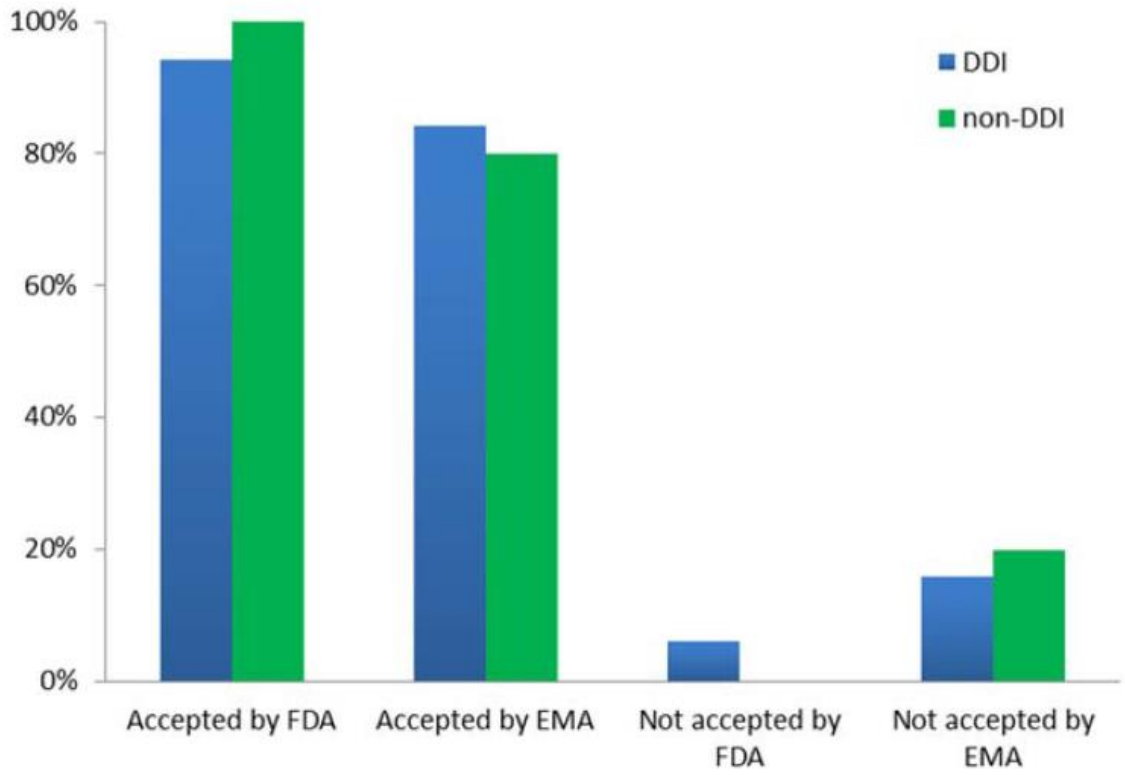
Type	No.	Examples
ANDA Reviews & Citizen petitions	22	❖ Implement clinical relevant PK metrics for BE assessment
Pre-ANDA interactions (including CC)	26	❖ Development of BE criteria for analgesics ❖ Assessment of BE standards for GI locally acting products ❖ Simulation of in vivo alcohol dose dumping studies
BE Guidances	31	❖ Simulations for the development of BE criteria for HVDs and NTI drugs
Regulatory Research Studies	30	❖ Pharmacokinetic(PK)/Pharmacodynamic (PD) modeling and simulation to determine the appropriate study design and evaluate clinical endpoint sensitivity for BE assessment

ANDA: abbreviated new drug application; BE: bioequivalence: CP: citizen petition; CC: controlled correspondence; GI: gastrointestinal; HVD: highly variable drugs; NTI: narrow therapeutic index.

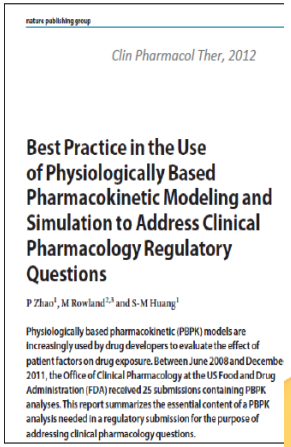
*https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM550577.pdf

Regulatory scientists trained on GastroPlus™ PBPK modeling

Rate of acceptance of PBPK analyses by FDA & EMA



Tour of the policy development in PBPK area


nature publishing group

Clin Pharmacol Ther, 2012

Best Practice in the Use of Physiologically Based Pharmacokinetic Modeling and Simulation to Address Clinical Pharmacology Regulatory Questions

P Zhao[1], M Rowland[2,3] and S-M Huang[1]

Physiologically based pharmacokinetic (PBPK) models are increasingly used by drug developers to evaluate the effect of patient factors on drug exposure. Between June 2008 and Decembe 2011, the Office of Clinical Pharmacology at the US Food and Drug Administration (FDA) received 25 submissions containing PBPK analyses. This report summarizes the essential content of a PBPK analysis needed in a regulatory submission for the purpose of addressing clinical pharmacology questions.

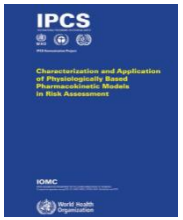
2010- WHO guidance

2012- Opinion paper from FDA

2014 FDA & EMEA workshops

2016 FDA & EMEA Draft guidance

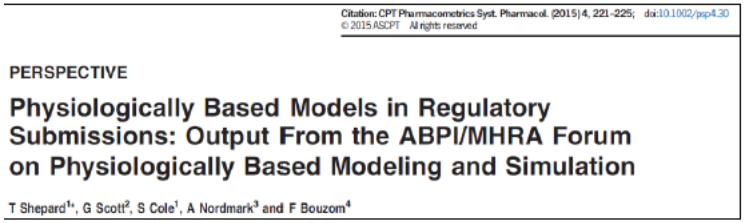
2018 FDA final guidance & EMEA Guidelines


IPCS

Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

IOMC

World Health Organization


Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 221–225; doi:10.1002/psp4.30
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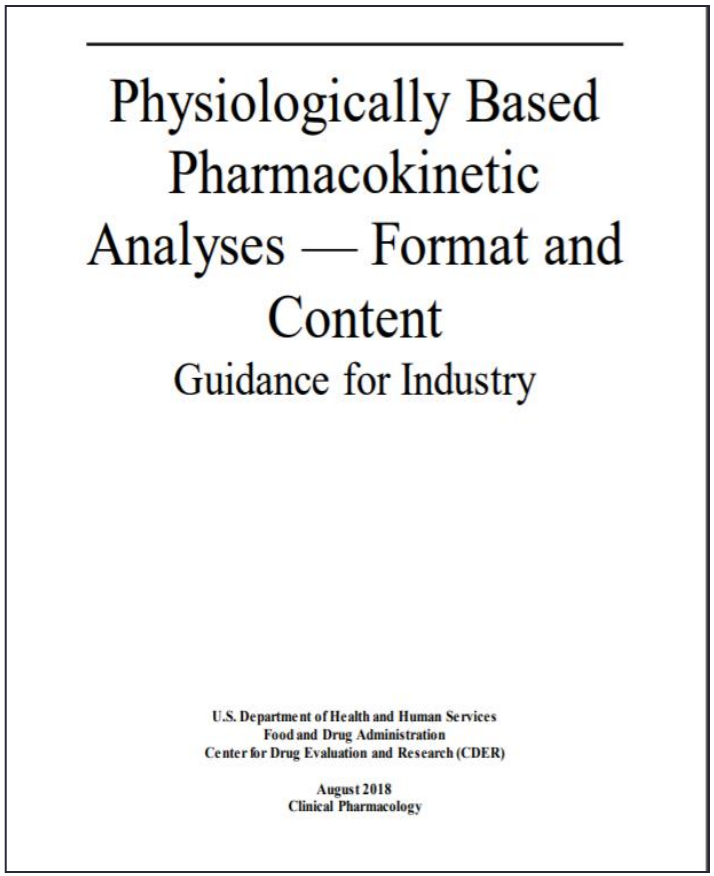
PERSPECTIVE

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

Regulatory guidelines

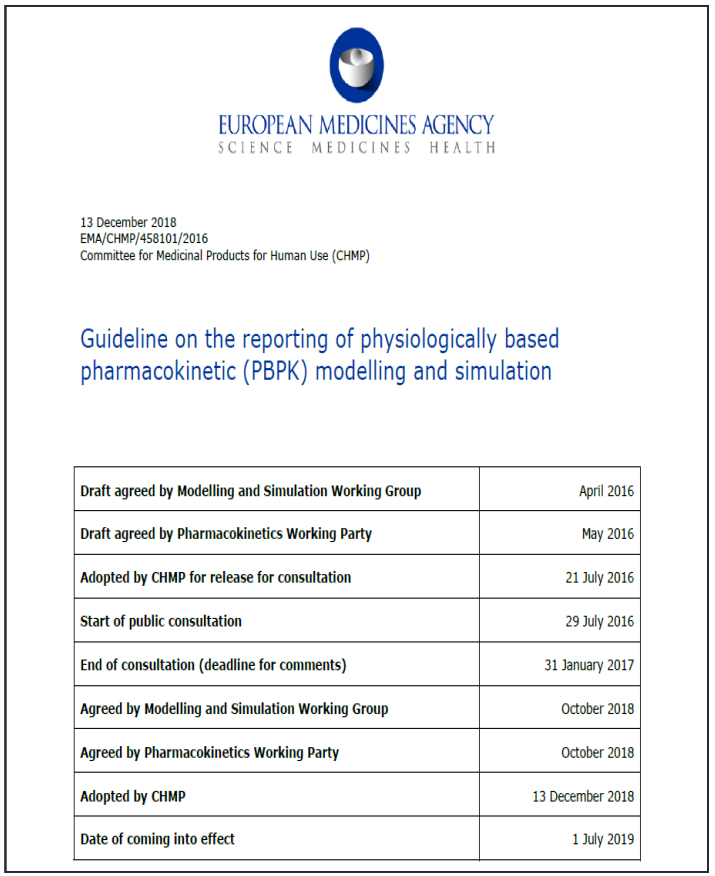


Physiologically Based Pharmacokinetic Analyses — Format and Content

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

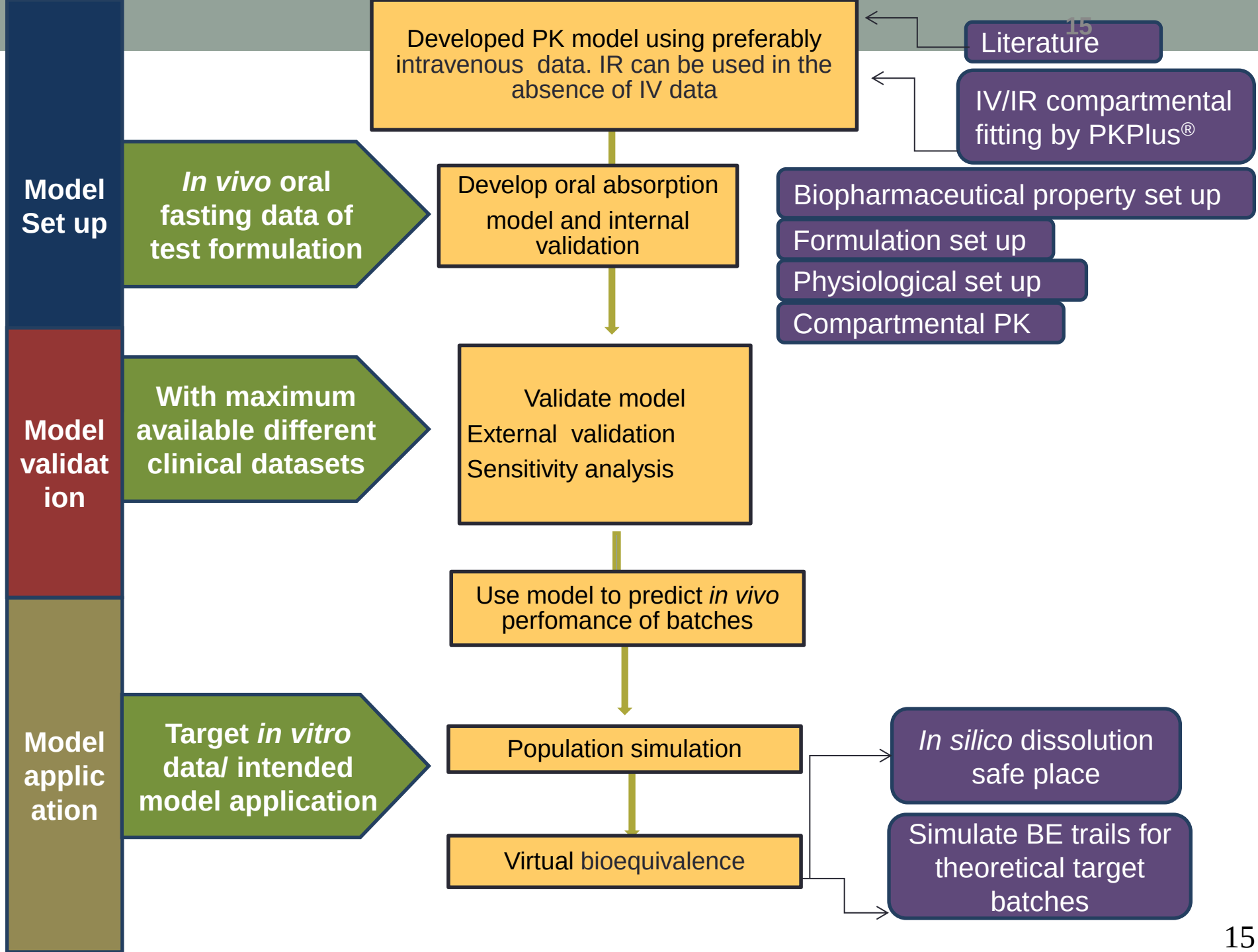
Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

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

*http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211315.pdf
*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf

Flow diagram of mechanistic modeling

Optimum blend of human intelligence and artificial intelligence is must..!!


Model Set up
Model validation
Model application
Developed PK model using preferably intravenous data. IR can be used in the absence of IV data
Literature
IV/IR compartmental fitting by PKPlus®
In vivo oral fasting data of test formulation
Develop oral absorption model and internal validation
Biopharmaceutical property set up
Formulation set up
Physiological set up
Compartmental PK
With maximum available different clinical datasets
Validate model
External validation
Sensitivity analysis
Use model to predict in vivo perfomance of batches
Target in vitro data/ intended model application
Population simulation
Virtual bioequivalence
In silico dissolution safe place
Simulate BE trails for theoretical target batches

Example 1: BCS class 2 drug formulated as MR tablet

Case:

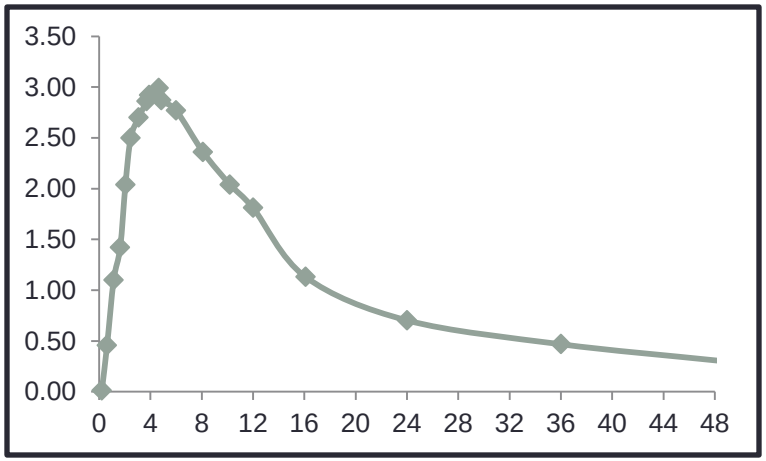
- Matrix based formulation in multiple strengths having low ISCV
- pH dependent solubility, lower solubility at acidic pH
- No food effect and **linear PK**
- Available data: Fasting, fed BE data for highest strength and one fed study data for lower strength, IR BE data.

Intended purpose of the simulation:

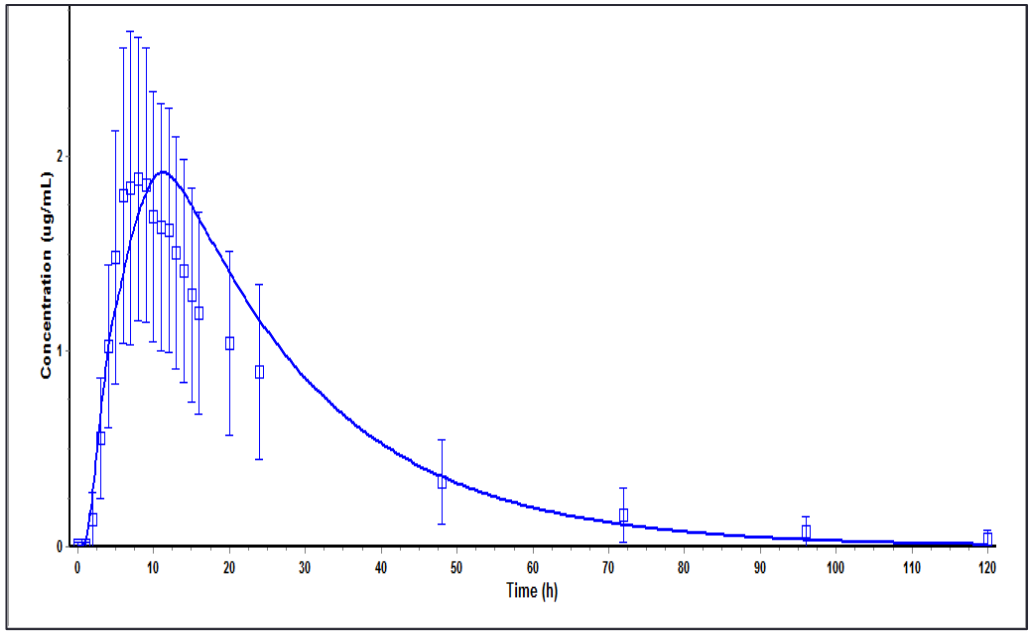
- Formulation composition was different for lower strength to match f_2 in dissolution. Agency requested to conduct additional BE studies for lower strength
- To assess the risk of not conducting additional BE study for the lower strength

Model development

Physiochemical Properties	Values
Molecular weight (g/mol)	Around 300
pKa	5.8 (basic)
P_{eff} (cm/sec)	3.3 X 10-4
log P	1.7
Dosage form	CR Integral Tablet
Dose volume (ml)	250
Aqueous solubility (mg/mL) @ pH 6.8	0.37



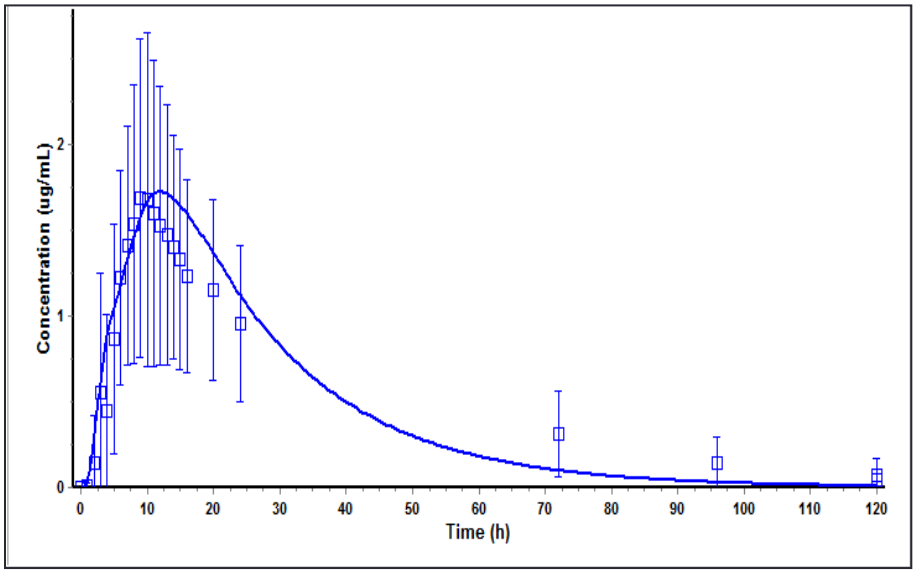
IR profile of the compound



Parameters	Observed	Predicted	% PE
C_{max} (ng/ml)	1.88	1.91	-1.77
T_{max}	8	11	
AUC_{0-t} (ng-h/ml)	53.45	56.40	-5.23
AUC_{0-inf} (ug-h/mL):	54.79	56.62	-3.23

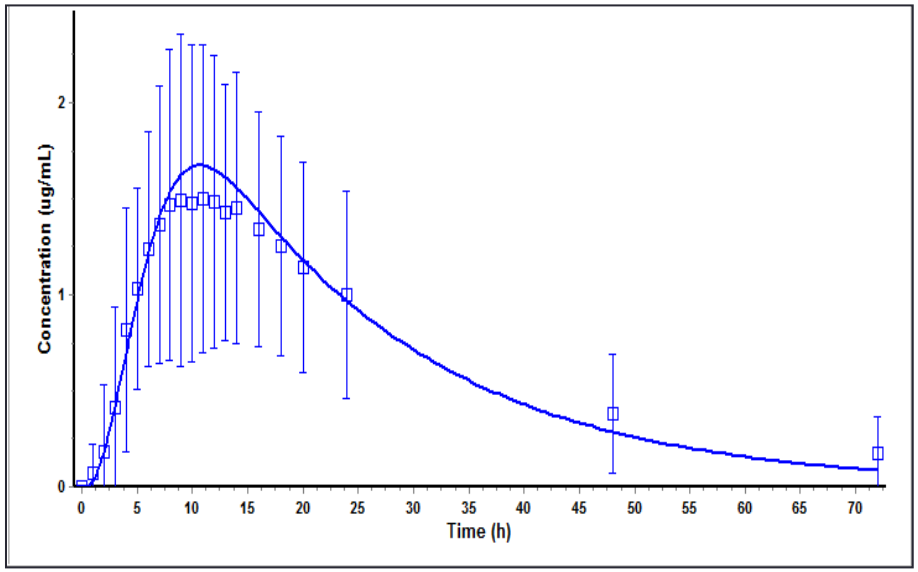
Model building with formulation AA, x mg, fasting

Model verification



Model verification with formulation AB x mg, fasting state

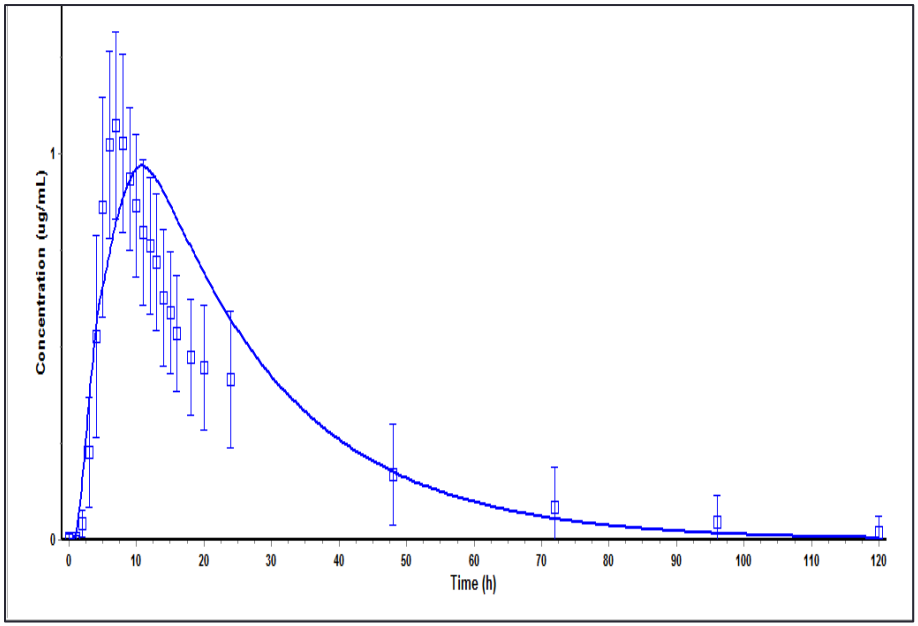
slower *in vitro* and *in vivo* release than the batch used in model building,



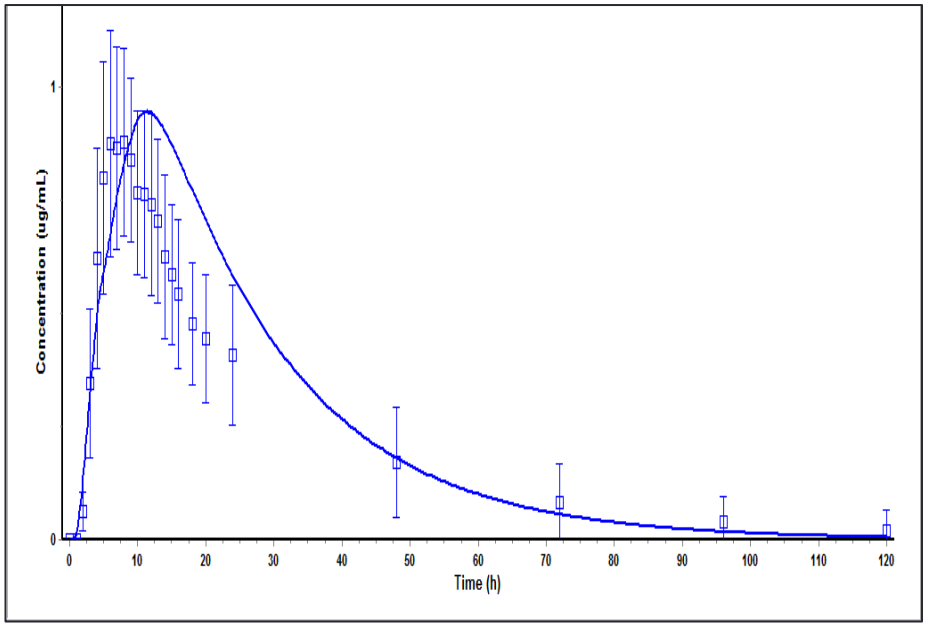
Model verification with Formulation AA, x mg, fed state

Model verification

Formulation A, 0.5 X mg, Fed



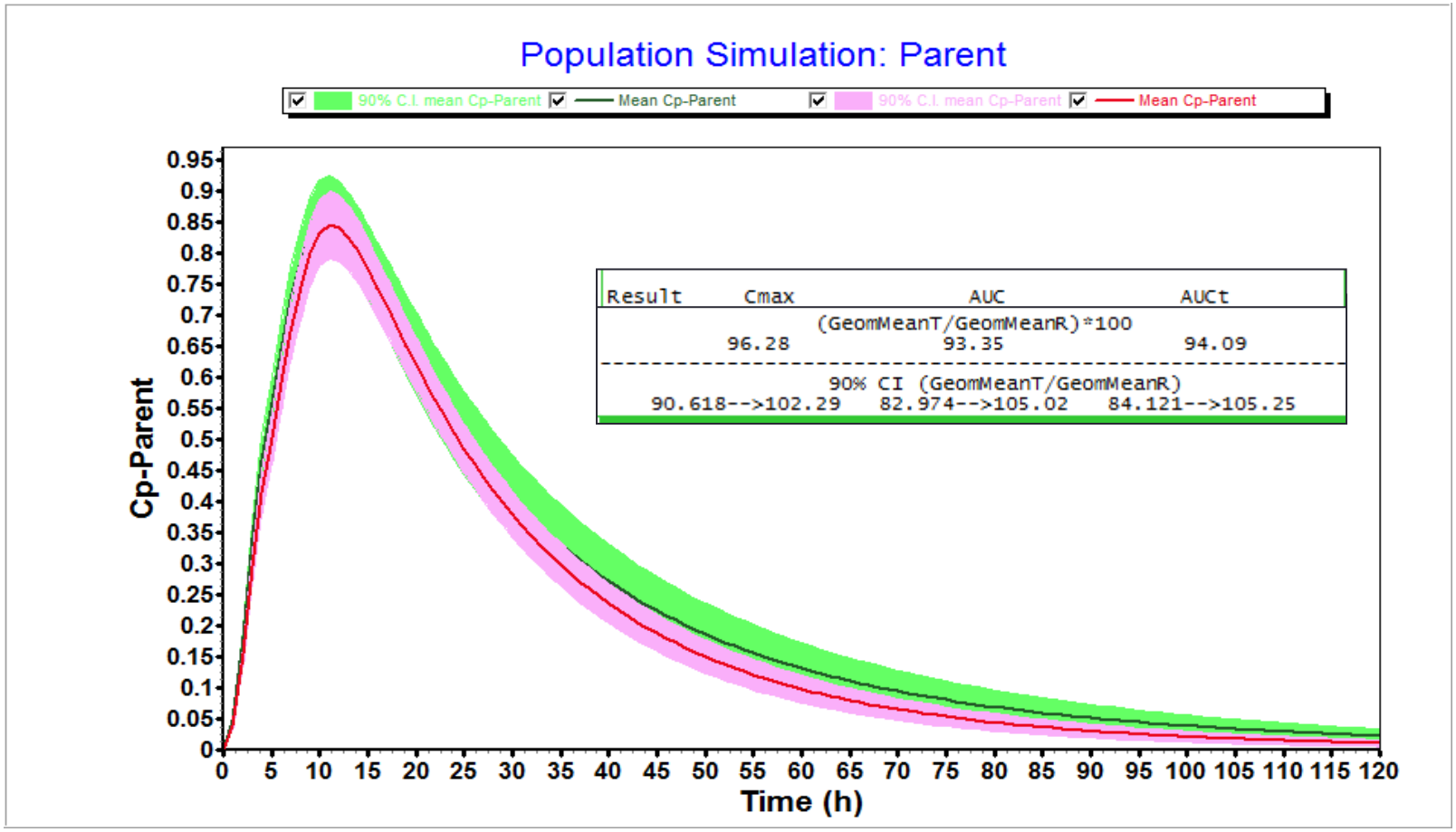
Formulation B, 0.5 X mg, Fed



Additional Verification of the model with different strength studies

Model application

Virtual BE of formulation A vs formulation B, 0.5xmg under fasting state



Example 1 Case conclusion

- ✓ The developed mechanistic absorption PK models described the key features in the PK curves under fasting and fed condition for both the strengths

- ✓ Mechanistic absorption modeling coupled with virtual BE was successfully employed to simulate PK profiles for lower strength having different composition under fasting state

Example 2: Evaluation of target particle size

Case: Compound was a weak base, BCS Class II, IR formulation, having pH dependent low solubility, Tmax-4h

Absorption Modeling Strategy: Simulation was used to predict the upper boundaries of the drug substance particle size distribution on *in vivo* performance of the drug product. Parameter sensitivity analysis was also done to identify the boundaries in which PSD will fail the BE and PSD which gives satisfactory results.

Outcome: This information and exploring these boundaries really helped with the future developments which reduced time and cost by waiving pilot studies

Example 3: Evaluation of clinically relevant specifications for BCS class III compound with non linear PK- ER formulation

Case: BCS III compound, ER formulation and pH independent high solubility across the pH

- Dose dependent bioavailability due to saturation of Pgp
- Very long half life & negative food effect
- Intended objective of simulation was widening of dissolution specifications

Absorption Modeling Strategy: The ACAT model was proposed to mechanistically predict drug dissolution and intestinal absorption including gut metabolism and active transport processes after oral administration.

- V_{max} and K_m values of the Pgp have been incorporated.
- Safe space determination
- Sensitivity analysis
- Virtual bioequivalence

Outcome: Mechanistic absorption model allowed IVIVR of the compound having non-linear PK

Proposed dissolution specification was found to produce bioequivalence between the pivotal test and reference formulations when simulated using crossover virtual trials in GastroPlus

Example 4: Evaluation of *in vivo* impact of slowing down dissolution with time

Case: To justify slow down of *in vitro* release observed over a time for BCS II drug having pH dependent solubility and long half life. Multimedia dissolution was performed. Slower release rate was observed at one of the conventional media.
Objective: Is it relevant to the product *in vivo* perfomance???

Absorption Modeling Strategy:

- Two compartment PK model fitted to IV data and validated using different set of available *in vivo* data.
- Z factor was fitted to slower (non-f2 matching) and normal dissolution profiles
- PSA and virtual BE trial

Outcome: Slower batch was found to produce bioequivalence between the pivotal test and reference formulations when simulated using crossover virtual trials in GastroPlus. *In vivo* study was conducted as a back up to evaluate *in vivo* impact. The results were inline with the simulated results.

Example 5: Evaluation of clinically relevant specifications for BCS class II compound- ER formulation

Case: To support wider dissolution specifications

BCS class II compound having pH dependent low solubility & high permeability, relatively high ISCV (30-35%) and short half-life (5-7 h)

Absorption Modeling Strategy: Same standard modeling practice has been followed which was explained earlier. Model was validated by 2 available different datasets. Model was also validated by published literature dataset. Virtual BE and PSA were then conducted to evaluate safe space.

Outcome: Proposed dissolution specification was found to produce bioequivalence between the pivotal test and reference formulations when simulated using crossover virtual trials in GastroPlus

Challenges

- ✓ Appropriate selection of input parameters
- ✓ Assumptions and optimization
- ✓ Model verification
- ✓ Lack of biorelevant *in vitro* methods
- ✓ Biopharmaceutics knowledge
- ✓ Excipient effects-better understanding of formulation perfomance *in vivo*
- ✓ Inclusion of CMA & CPP parameters in the commercially available software
- ✓ Identification and transparent communication of knowledge gaps
- ✓ Clarity on regulatory expectations

Summary

- ✓ Models that guide formulation selections or subsequent formulation modifications, such as API particle size or release rates for modified-release formulations, are routinely applied in early development
- ✓ Establishing confidence in physiological model is crucial for effective use of PBPK
- ✓ A well qualified model with high confidence can be used to aid regulatory decision-making
- ✓ Mechanistic Absorption/PK/PBPK in generic drug product development is still underutilized tool in the industry

Looking to the future

- ✓ Development and refinement of guidelines and recommendations for more efficient reporting of model results for regulatory submissions is mandatory

- ✓ The adoption of these harmonized practices will result in better decision-making, ultimately will lead to improved patient outcomes with the development of safe and efficacious drugs.


Thank you