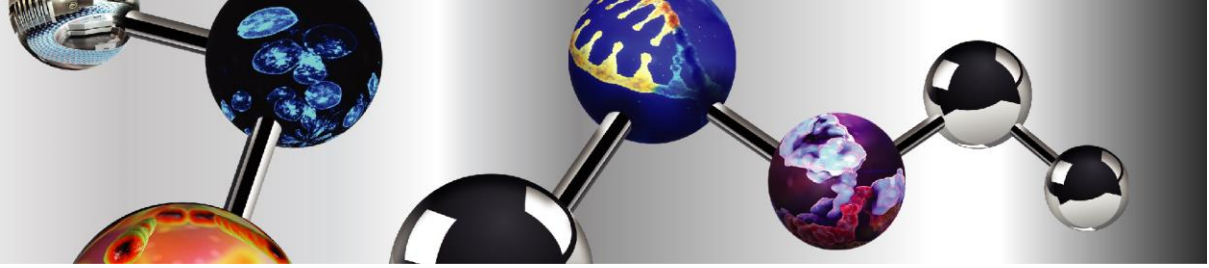
aaps PharmSci 360 OCT 17-20 2021



MIDD in Preclinical Drug Development

Providing a case for why you should focus on preclinical verification when using Physiologically Based Pharmacokinetic (PBPK) modeling for First-In-Human (F.I.H) pharmacokinetic predictions.

On Demand

Neil A. Miller, MSc

SimulationsPlus

SCIENCE + SOFTWARE = SUCCESS

Session Description and Objectives

Description:

- Provide a case for why you should focus on preclinical verification when using Physiologically Based Pharmacokinetic (PBPK) modeling for First-In-Human (F.I.H) pharmacokinetic predictions

Objectives:

- Appreciate that PBPK models are complex and combine systems physiology and drug specific input data
- Understand that verification of PBPK models in preclinical R&D assesses whether the combination of physiology and drug specific input data works for a specific drug
- Acknowledge that you should be realistic with your expectations and learn from poor predictions

Biography and Contact Information

- **Neil A. Miller** Vice President for Simulation Sciences, Simulations Plus
  - neil@simulations-plus.com
- Drive the development and application of physiologically based pharmacokinetic (PBPK) modeling software tools across the pharmaceutical industry
- Previously worked at GlaxoSmithKline for 24 years and was a Scientific Director leading a team of advanced PBPK specialists that provided end-to-end mechanistic modelling for drug discovery and development
- Passion for modeling and simulation, specializing in predicting human pharmacokinetics from preclinical data
- Believe that PBPK models should be in place for all compounds prior to *in vivo* studies in a “model first experiment later” paradigm

Aim of presentation

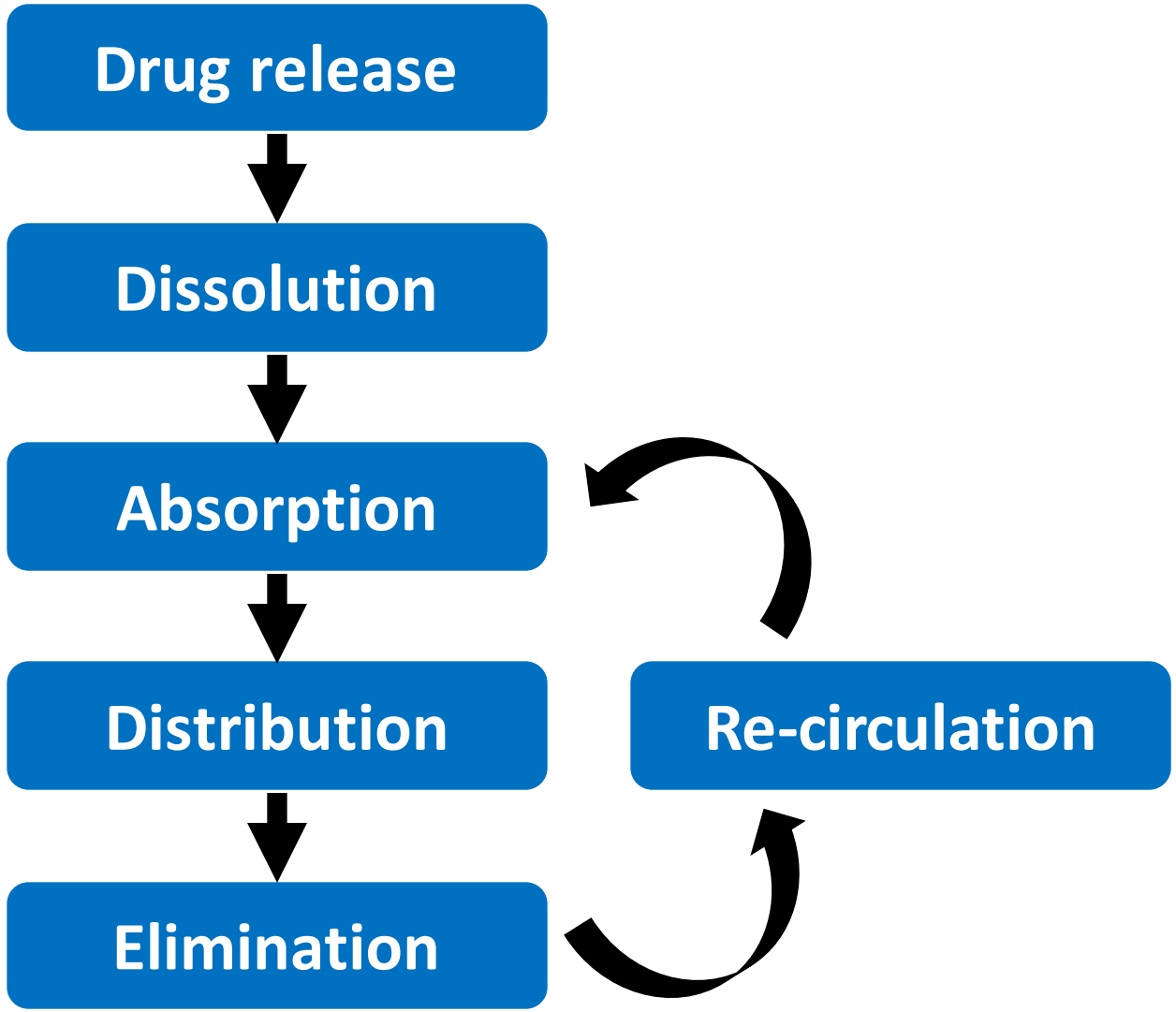
- Highlight that PBPK modeling can be used for Model-Informed Drug Development at the First-In-Human (F.I.H) stage, with verification of predictive performance first performed in preclinical species

- Emphasize that the verification of predictive performance should be both methodical and consistent across the industry

Learning Objectives

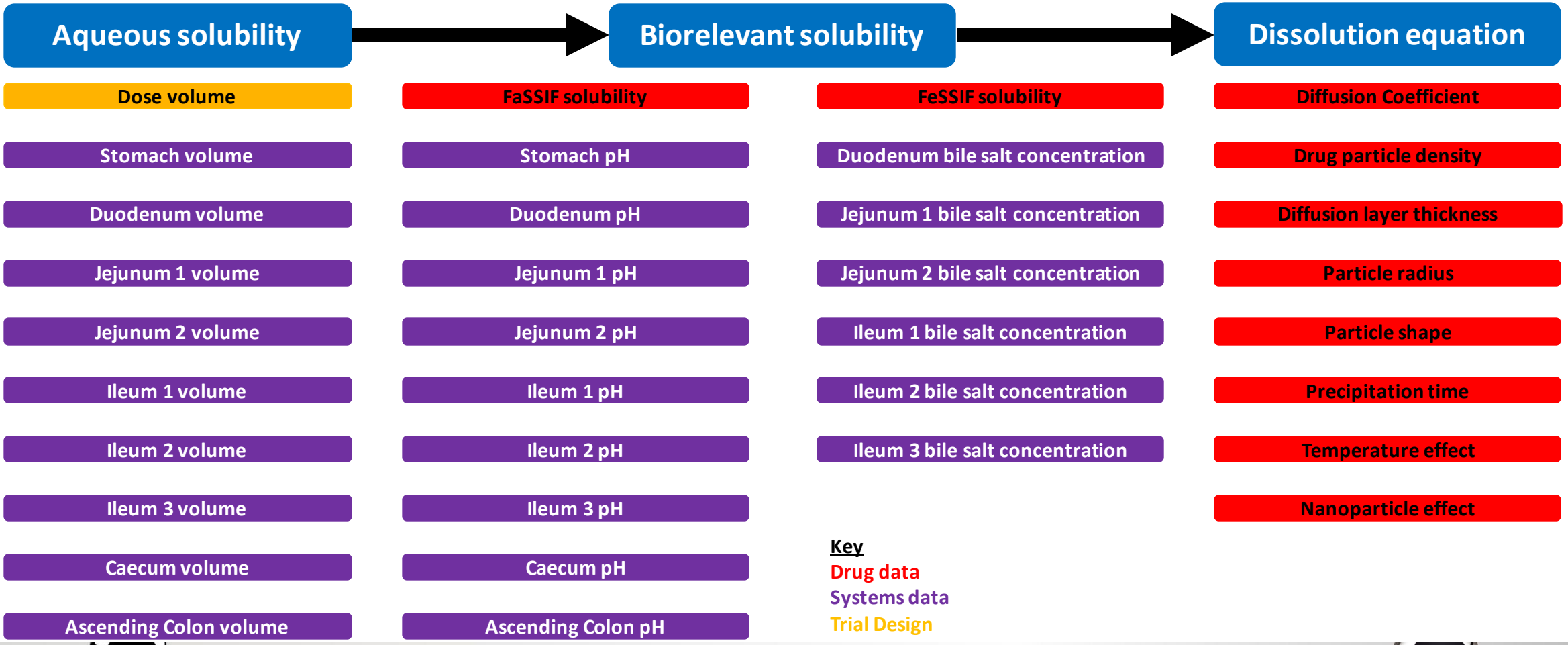
- Appreciate that PBPK models are complex and combine systems physiology with drug specific input data
- Understand that verification of PBPK models in preclinical R&D assesses whether the combination of physiology and drug specific input data works for a specific drug
- Acknowledge that you should be realistic with your expectations and learn from poor predictions

F.I.H PBPK model = Sum of mechanisms



Let's focus on one mechanism: Dissolution

- Three main aspects of dissolution, but many many details!



But you can't focus on one mechanism

- Because mechanisms are intimately interconnected and explicable only by reference to the whole

- Let's break this down and take it slowly to avoid confusion:
  - Drug dissolution depends on local GI concentration which depends on absorption …
  - … which depends on systemic distribution …
  - … which depends on systemic elimination …
  - … which depends on systemic distribution and absorption!

But you can't focus on one mechanism

- Drug dissolution depends on local GI concentration which depends on absorption …
  - *i.e., when drug is absorbed it lowers the local GI concentration and this encourages dissolution*
- … which depends on systemic distribution …
  - *i.e., when drug is distributed it lowers the concentration in blood and this encourages absorption*
- … which depends on systemic elimination …
  - *i.e., when drug is eliminated it is gone from the body and can't distribute to tissues*
- … which depends on systemic distribution and absorption!
  - *i.e., only drug that has been absorbed and is not distributed to tissues can be eliminated*

  (note that following oral administration some drug can be excreted from the GI tract without being absorbed)

The reality of the situation part I

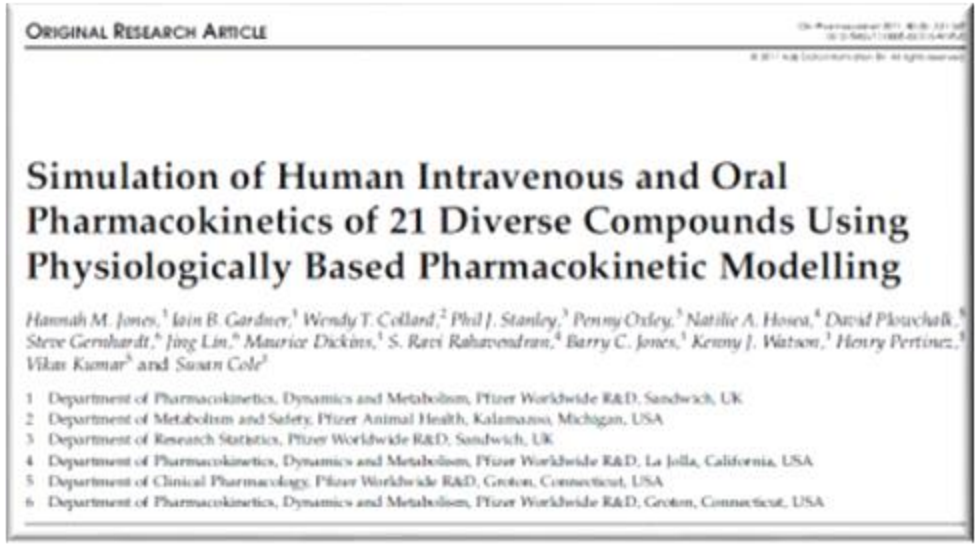
PBPK models are complex as they combine many systems physiology and drug and formulation specific input data

Drug specific parameters and systems physiology parameters are intimately interconnected and explicable only by reference to the whole

To increase confidence in the whole you need verification of the PBPK model in preclinical species

There is also a moral obligation to get the most out of the preclinical data as animals have been sacrificed to develop the drug for humans

Proof PBPK works for F.I.H PK predictions



ORIGINAL RESEARCH ARTICLE

Simulation of Human Intravenous and Oral Pharmacokinetics of 21 Diverse Compounds Using Physiologically Based Pharmacokinetic Modelling

Hannah M. Jones,[1] Iain B. Gardner,[1] Wendy T. Collard,[2] Phil J. Stanley,[3] Penny Oxley,[3] Natalie A. Hosea,[4] David Plowchalk,[5] Steve Gernhardt,[5] Jing Lin,[6] Maurice Dickins,[1] S. Ravi Rahavendran,[4] Barry C. Jones,[1] Kenny J. Watson,[1] Henry Pertinez,[1] Vikas Kumar[3] and Susan Cole[3]

1 Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Worldwide R&D, Sandwich, UK
2 Department of Metabolism and Safety, Pfizer Animal Health, Kalamazoo, Michigan, USA
3 Department of Research Statistics, Pfizer Worldwide R&D, Sandwich, UK
4 Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Worldwide R&D, La Jolla, California, USA
5 Department of Clinical Pharmacology, Pfizer Worldwide R&D, Groton, Connecticut, USA
6 Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Worldwide R&D, Groton, Connecticut, USA

RESEARCH ARTICLE – *Drug Discovery-Development Interface*

Prospective Predictions of Human Pharmacokinetics for Eighteen Compounds

TAO ZHANG, TYCHO HEIMBACH, WEN LIN, JIN ZHANG, HANDAN HE

Drug Metabolism and Pharmacokinetics, Novartis Institutes for Biomedical Research, East Hanover, New Jersey 07936

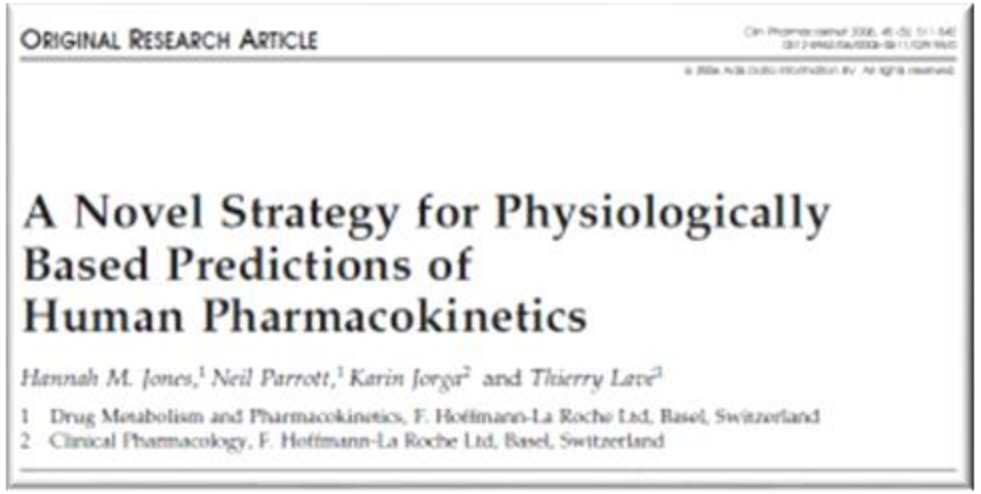
Received 26 August 2014; revised 2 January 2015; accepted 8 January 2015

Published online 17 February 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24373

Pfizer "The simulation results using PBPK were shown to be superior to those obtained via traditional one compartment analyses. In many cases, this difference was statistically significant."

Novartis "Our prospective human PK prediction methods yielded good prediction results."

Proof PBPK works for F.I.H PK predictions



ORIGINAL RESEARCH ARTICLE

A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics

Hannah M. Jones,[1] Neil Parrott,[1] Karin Jorga[2] and Thierry Lave[2]

1 Drug Metabolism and Pharmacokinetics, F. Hoffmann-La Roche Ltd, Basel, Switzerland
2 Clinical Pharmacology, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Prediction of Human Pharmacokinetics Using Physiologically Based Modeling: A Retrospective Analysis of 26 Clinically Tested Drugs

Stefan S. De Buck, Vikash K. Sinha, Luca A. Fenu, Marjoleen J. Nijsen, Claire E. Mackie, and Ron A. H. J. Gilissen

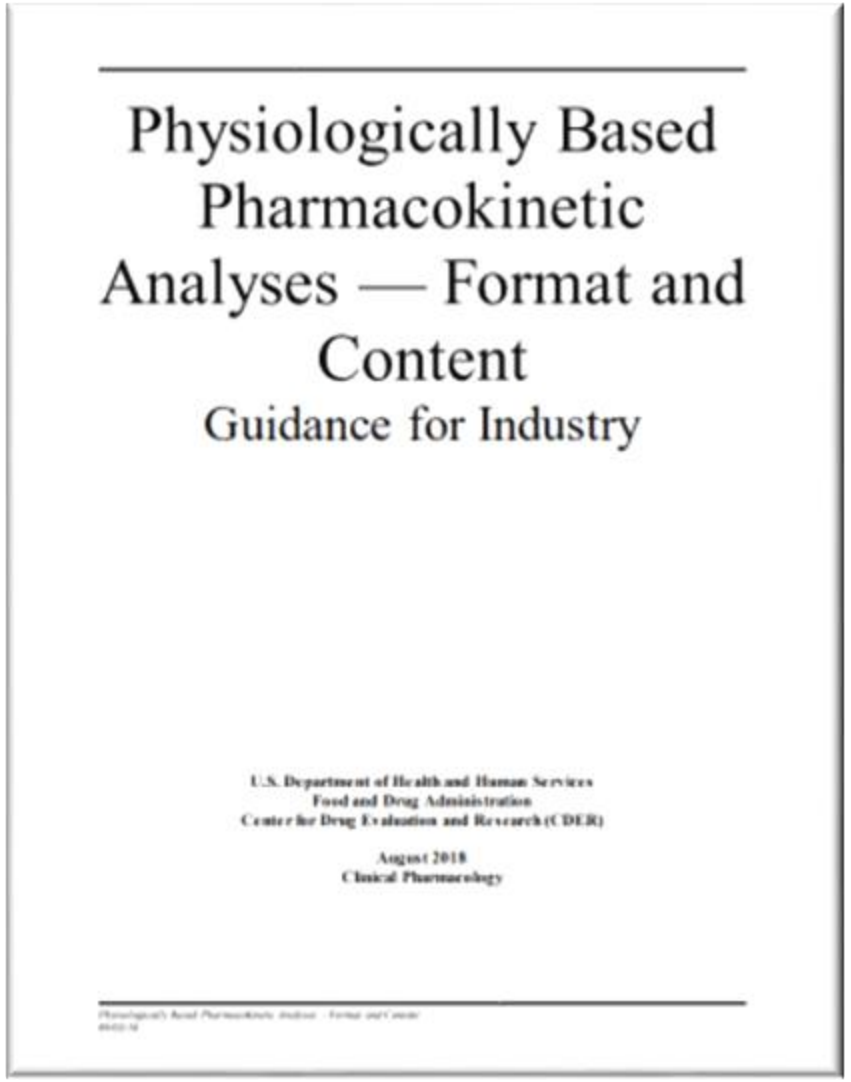
Johnson & Johnson Pharmaceutical Research and Development, Discovery ADME-Tox Department, Beerse, Belgium

Received March 5, 2007; accepted July 3, 2007

Roche "In the majority of cases, PBPK gave more accurate predictions of pharmacokinetic parameters and plasma concentration-time profiles than the Dedrick approach."

Johnson & Johnson "This evaluation demonstrates that PBPK models can lead to reasonable predictions of human pharmacokinetics."

Regulatory Guidance for PBPK modeling



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

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

What the doubters may say

"*Possibly* for passive distribution, but *not* when transporters are involved"

"Could lead and inform, but *not* verify"

"Animal empirical adjustments may or *may not* work for humans"

The reality of the situation part II

- PBPK models will not adequately predict all the time!
  - Aiming to be adequate not perfect = within two-fold for parameters or within the correct category

- When a PBPK model does not predict then the learning begins!
  - Are one of the input parameters wrong?
  - Is there a mechanism missing?

Adequate prediction

- Within two-fold for parameters or within the correct category…
  - Clearance categories:

    Low (<1/3 LBF), moderate (1/3 LBF – 2/3 LBF) or high (>2/3 LBF)

    LBF = Liver Blood Flow

  - Volume of Distribution categories:

    Small (<0.6 L/kg TBW), moderate (0.6 – 2.0 L/kg) or large (> 2.0 L/kg)

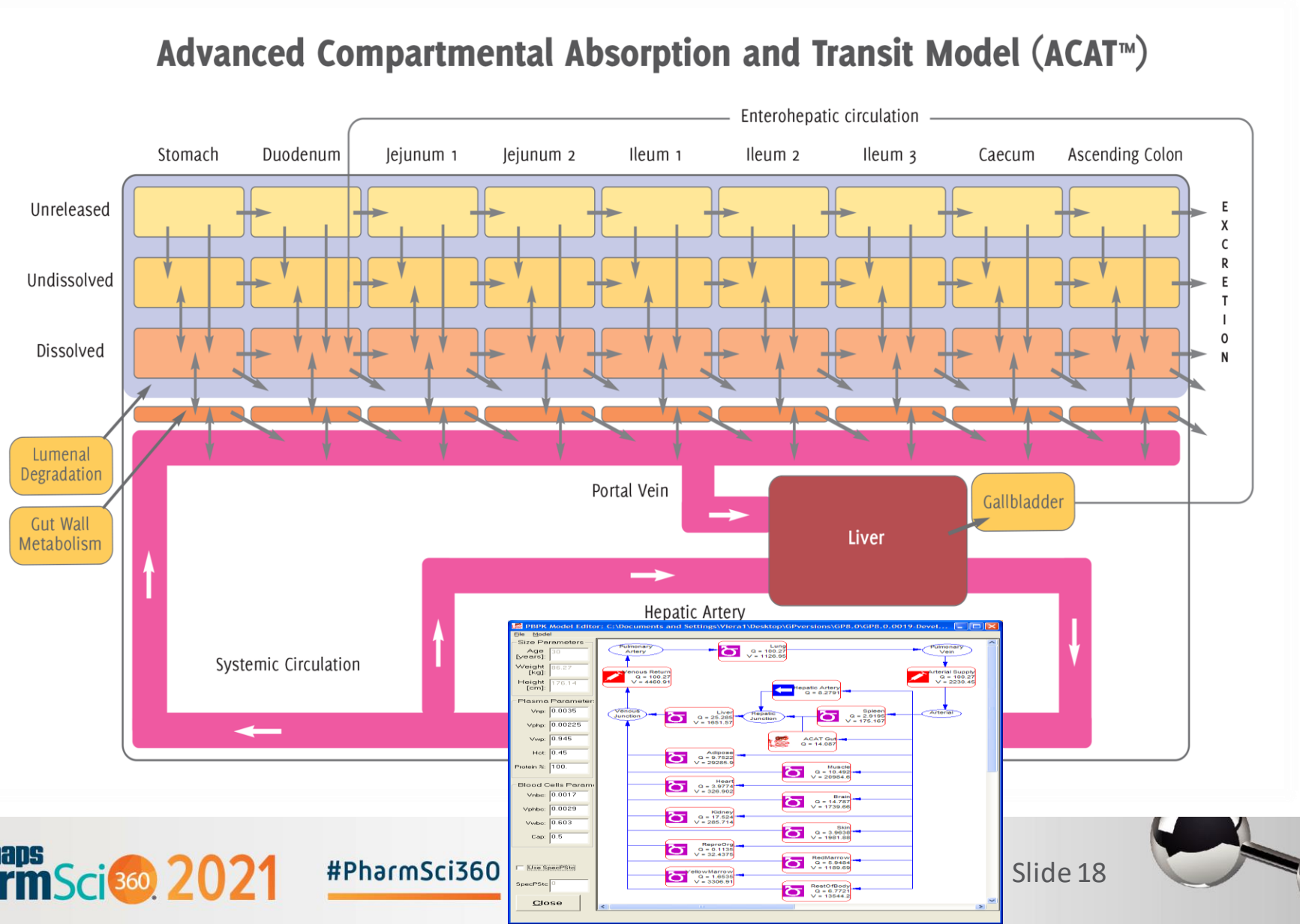
    TBW = Total Body Water

Key components of a F.I.H PK prediction for oral administration

- **Oral Absorption**
  - Multifactorial process driving drug reaching the systemic circulation
- **Distribution**
  - Using mechanistic tissue partitioning equations
- **Metabolism and Elimination**
  - Quantitative understanding of the main mechanism(s) of drug clearance

F.I.H PK prediction = ACAT + Systemic PBPK

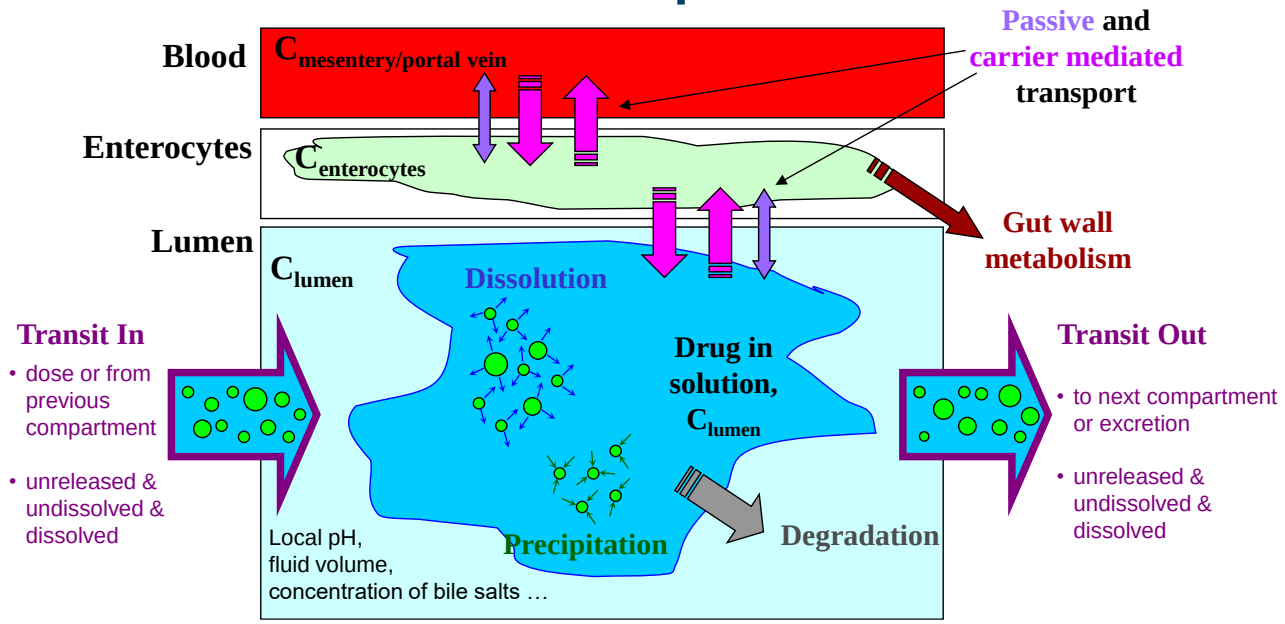
30,000 foot view



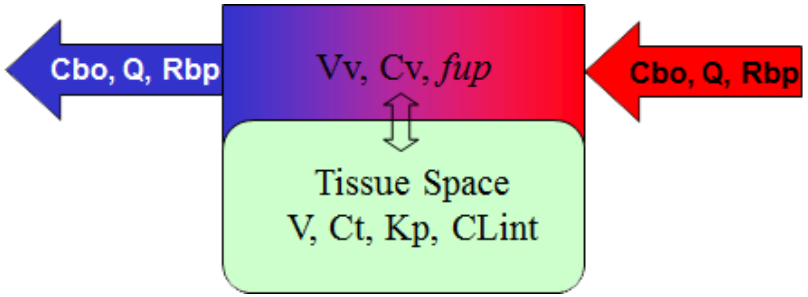
F.I.H PK prediction = ACAT + Systemic PBPK

Ground level view

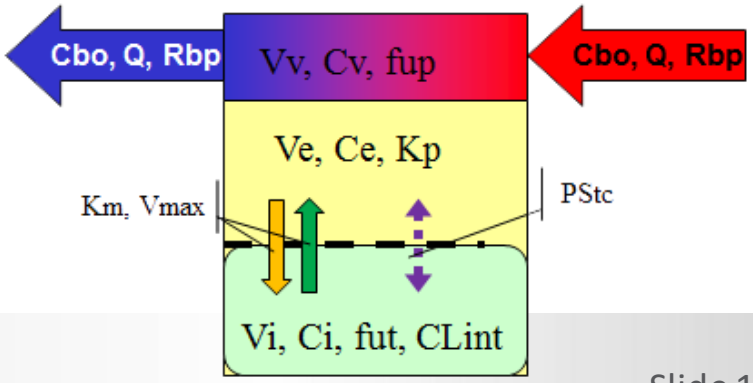
ACAT compartment



Perfusion-limited tissue



Permeability-limited tissue



An industry defined F.I.H PBPK strategy

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

REVIEW ARTICLE

Check for updates

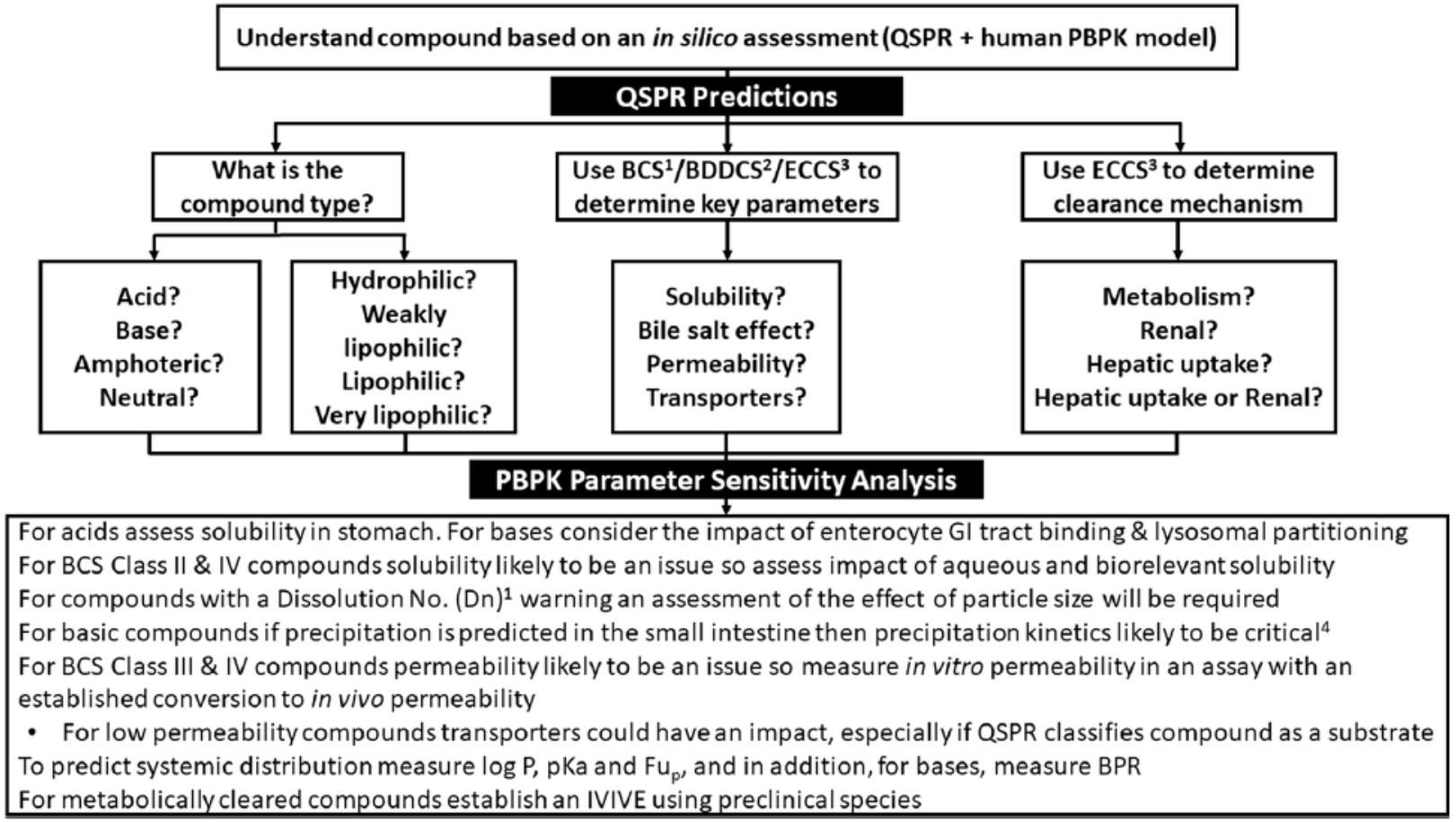
Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies

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

Published online: 7 February 2019

- Flow diagrams for each essential component of a F.I.H prediction using PBPK modeling!
- Flow diagrams include empirical fitting so there is still work to do for PBPK modelers!

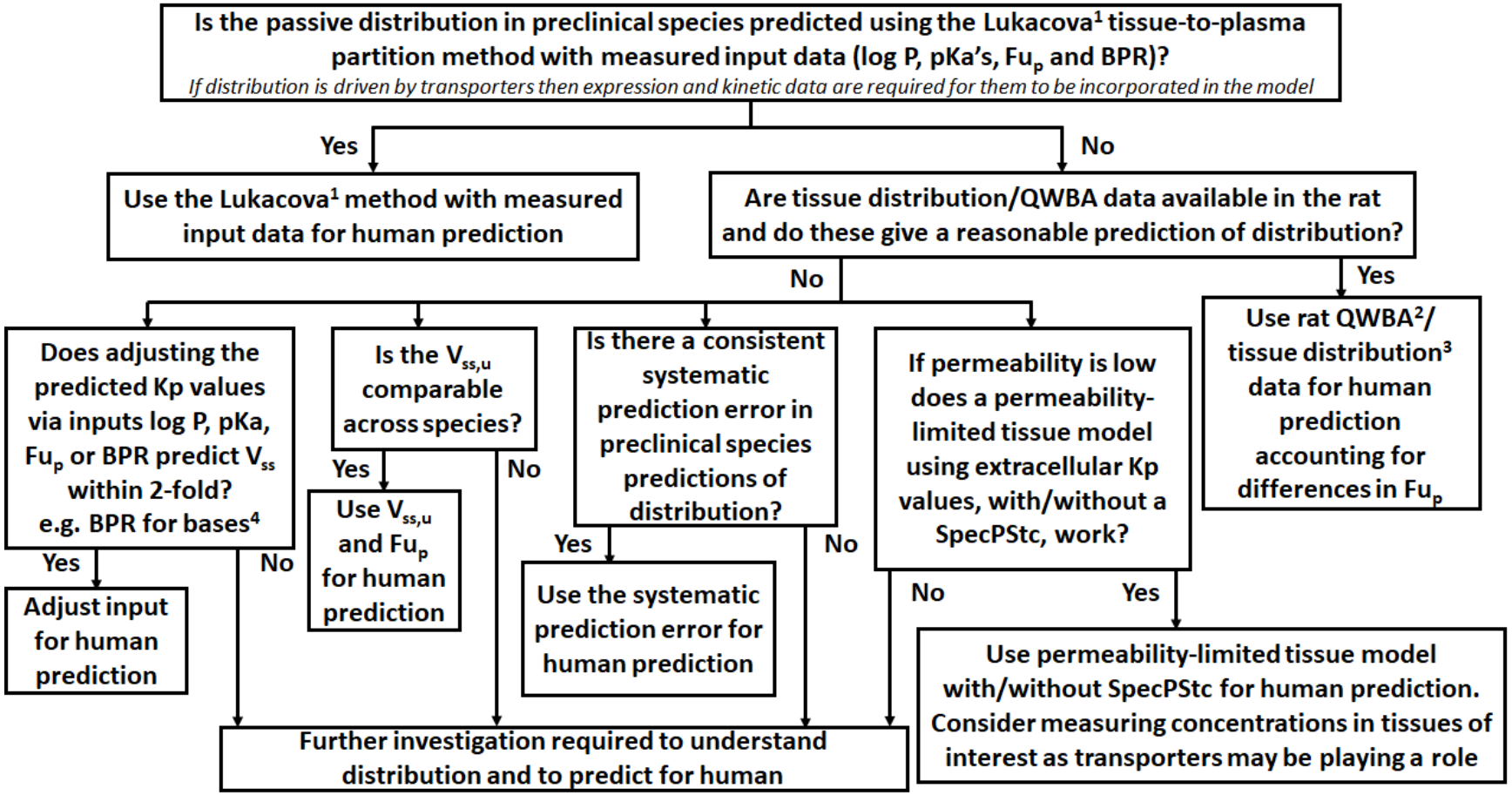
Start with QSPR + PBPK



Quantitative structure– property relationship (QSPR) plus physiologically based pharmacokinetic (PBPK) modelling

BCS Biopharmaceutics Classification System, BDDCS Biopharmaceutics Drug Disposition Classification System, BPR blood/plasma ratio, Dn dissolution number (the ratio of small intestine transit time/idealised dissolution time), ECCS Extended Clearance Classification System, Fup Fraction unbound in plasma, GI gastrointestinal, IVIVE in-vitro in-vivo extrapolation

Distribution



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[2]Xia B, Heimbach T, Lin TH, He H, Wang Y, Tan E. Novel physiologically based pharmacokinetic modeling of patupilone for human pharmacokinetic predictions. Cancer Chemother Pharmacol. 2012;69(6):1567–82.
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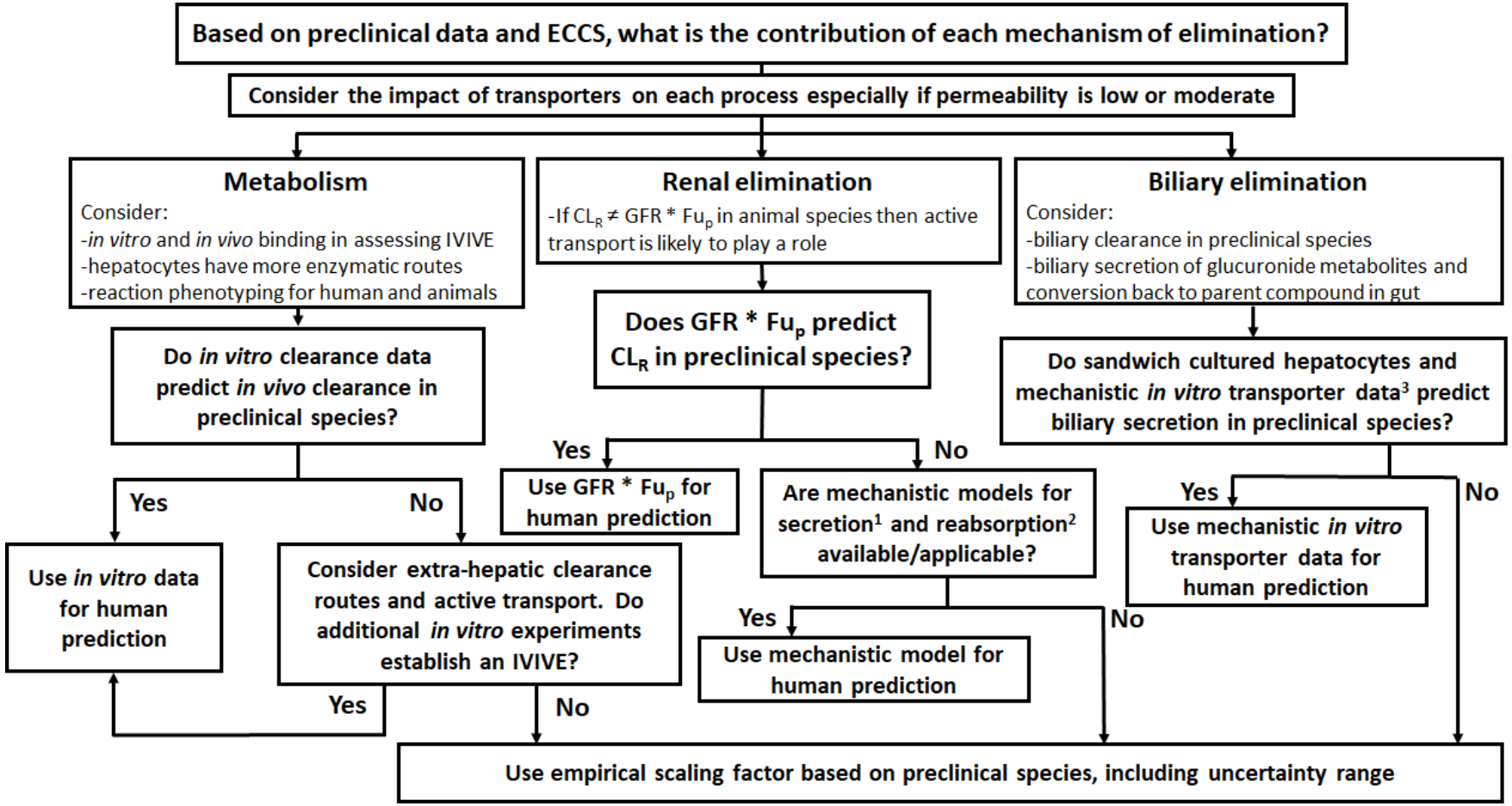
[4]Samant TS, Lukacova V, Schmidt S. Development and qualification of physiologically based pharmacokinetic models for drugs with atypical distribution behavior: a desipramine case study. CPT Pharmacometrics Syst Pharmacol. 2017;6(5):315–21.

BPR blood/plasma ratio, Fup fraction unbound in plasma, Kp tissue-to-plasma partition coefficient, QWBA Quantitative Whole Body Autoradiography, SpecPStc specific in-vivo diffusional clearance per millilitre of tissue cell volume.

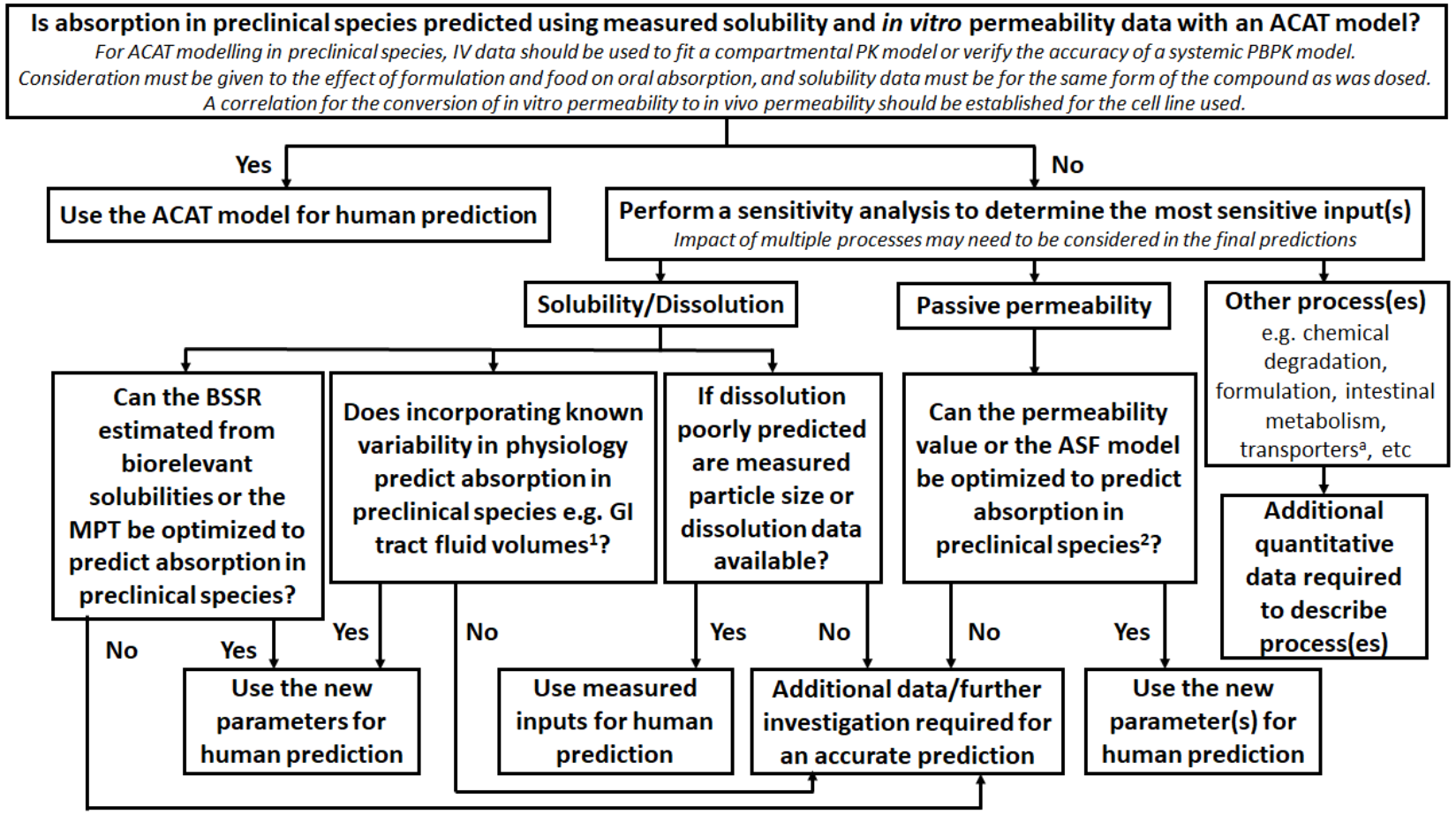
Metabolism and Elimination



[1]Mathialagan S, Piotrowski MA, Tess DA, Feng B, Litchfield J, Varma MV. Quantitative prediction of human renal clearance and drug-drug interactions of organic anion transporter substrates using in vitro transport data: a relative activity factor approach. Drug Metab Dispos. 2017;45(4):409–17.
[2]Scotcher D, Jones C, Rostami-Hodjegan A, Galetin A. Novel minimal physiologically-based model for the prediction of passive tubular reabsorption and renal excretion clearance. Eur J Pharm Sci. 2016;94:59–71.
[3]Kimoto E, Bi YA, Kosa RE, Tremaine LM, Varma MVS. Hepatobiliary clearance prediction: species scaling from monkey, dog, and rat, and in vitro-in vivo extrapolation of sandwich-cultured human hepatocytes using 17 drugs. J Pharm Sci. 2017;106(9):2795–804.

CL_R renal clearance, $CL_{R,u}$ unbound renal clearance, ECCS Extended Clearance Classification System, Fup fraction unbound in plasma, GFR glomerular filtration rate, IVIVE *in-vitro in-vivo* extrapolation.

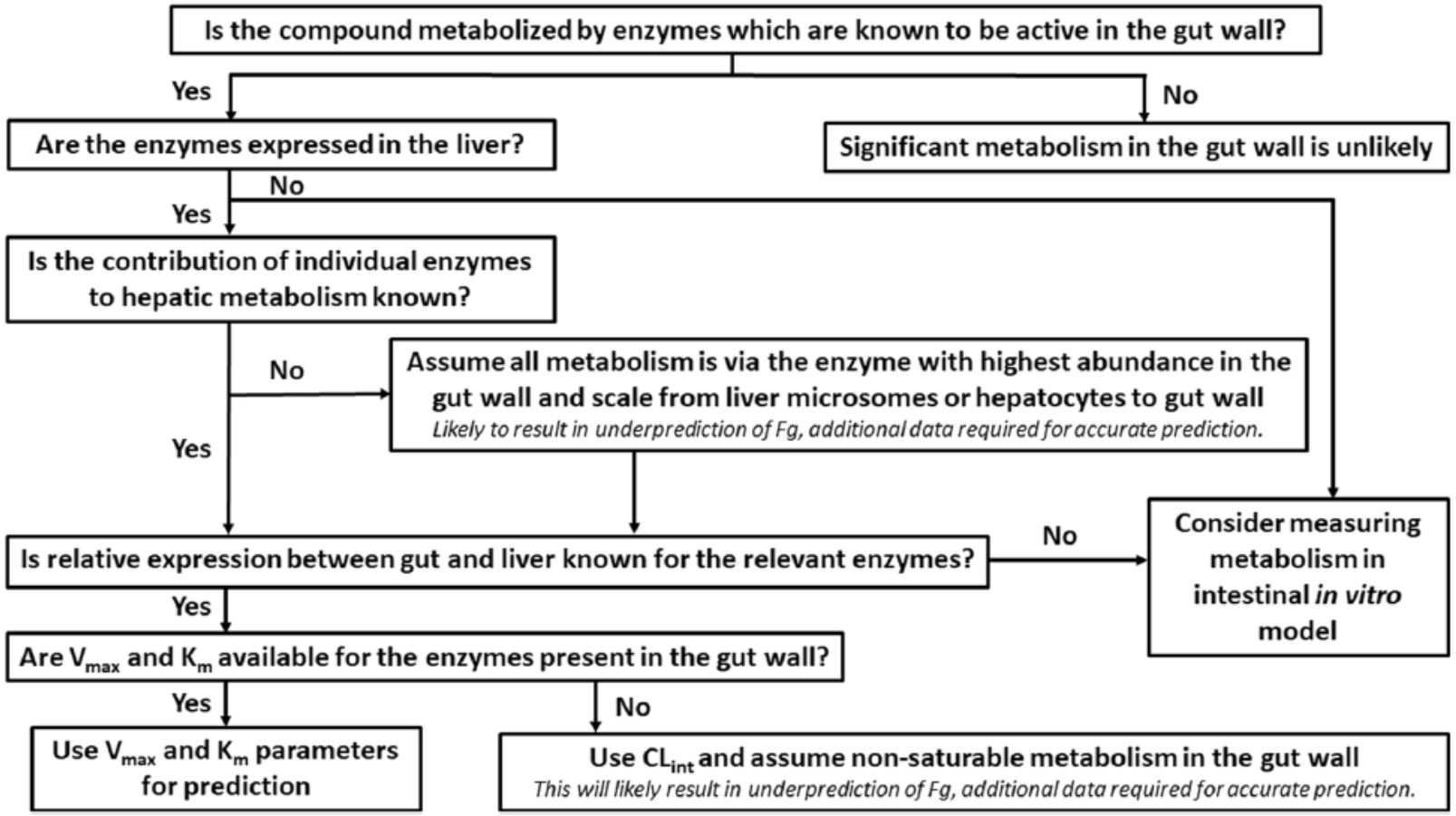
Oral absorption



[1]Sutton SC. Role of physiological intestinal water in oral absorption. AAPS J. 2009;11(2):277–85.
[2]Kesisoglou F. Use of preclinical dog studies and absorption modelling to facilitate late stage formulation bridging for a BCS II drug candidate. AAPS PharmSciTech. 2014;15(1):20–8.

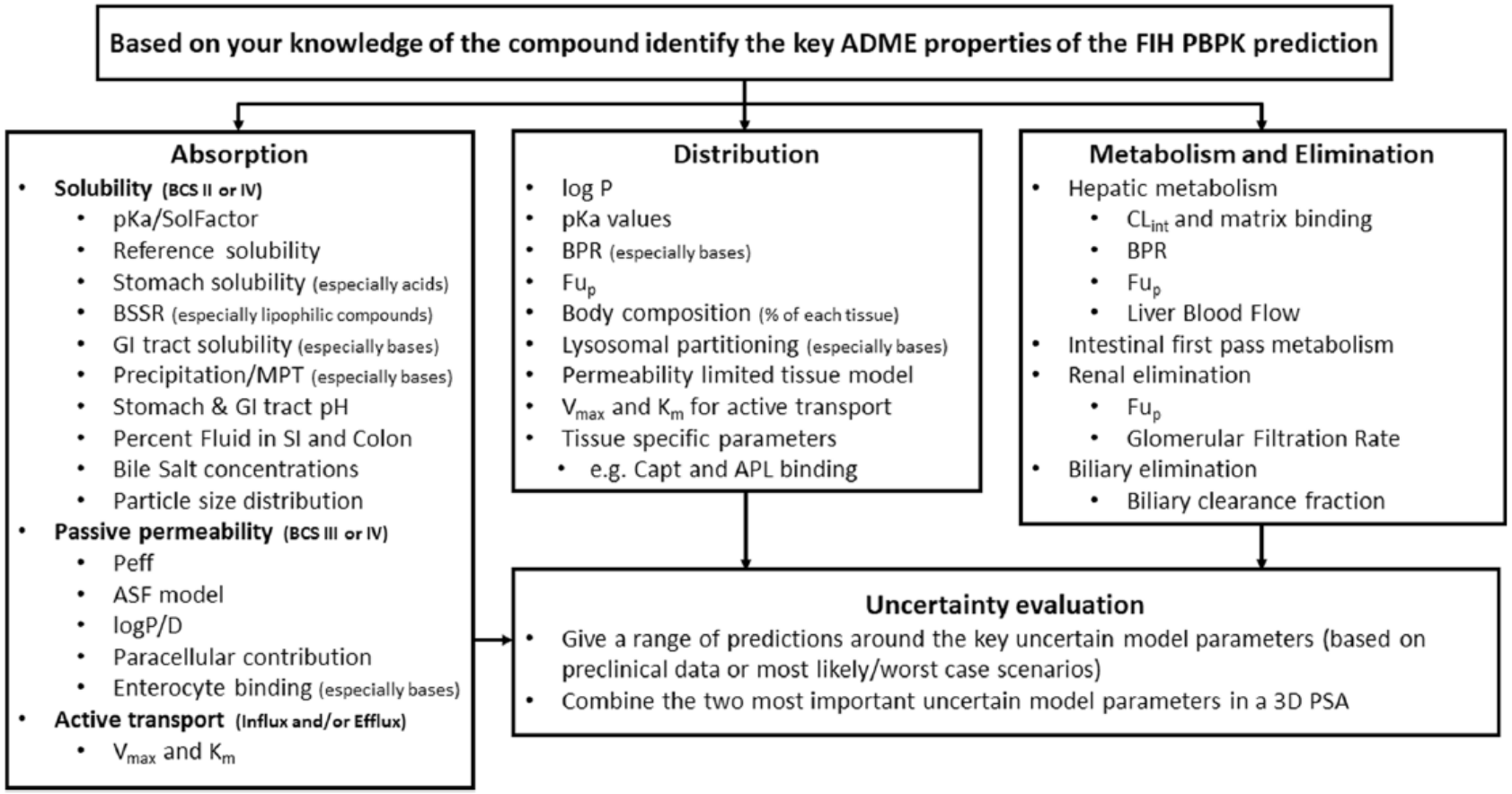
ASF absorption scale factors, BSSR bile salt solubilisation ratio, MPT mean precipitation time. [a] Other processes-transporters: efflux transporters can be incorporated in GastroPlus models with a simple method (e.g. adjusting permeability based on preclinical observations or in-vitro data) to more complex methods (e.g. specifically incorporating effects of transporters).

Gut wall metabolism



CL_{int} hepatic intrinsic clearance, Fg fraction of drug escaping gut wall metabolism, K_m concentration of substrate at half V_{max}, V_{max} maximum velocity or rate of enzyme catalyzed reaction.
Note: Gut wall metabolism is often saturable, and thus if V_{max} and K_m parameters are available, evaluate saturation relative to dose.

You must always include uncertainty



ADME Absorption, Distribution, Metabolism and Excretion, APL acidic phospholipid, ASF absorption scale factors, BCS Biopharmaceutics Classification System, BPR blood/plasma ratio, BSSR bile salt solubilization ratio, Capt concentration of acidic phospholipids in tissue, CLint hepatic intrinsic clearance, FIH first-in-human, Fup fraction unbound in plasma, Km concentration of substrate at half Vmax, MPT mean precipitation time, PSA parameter sensitivity analysis, Peff effective permeability, SI small intestine, SolFactor solubility factor, Vmax maximum velocity or rate of enzyme catalyzed reaction

Industry case study

- Real-world example of how PBPK was applied for FIH PK
- Drug with challenging properties
- Focus on accuracy **and** learning gained

Drug in question

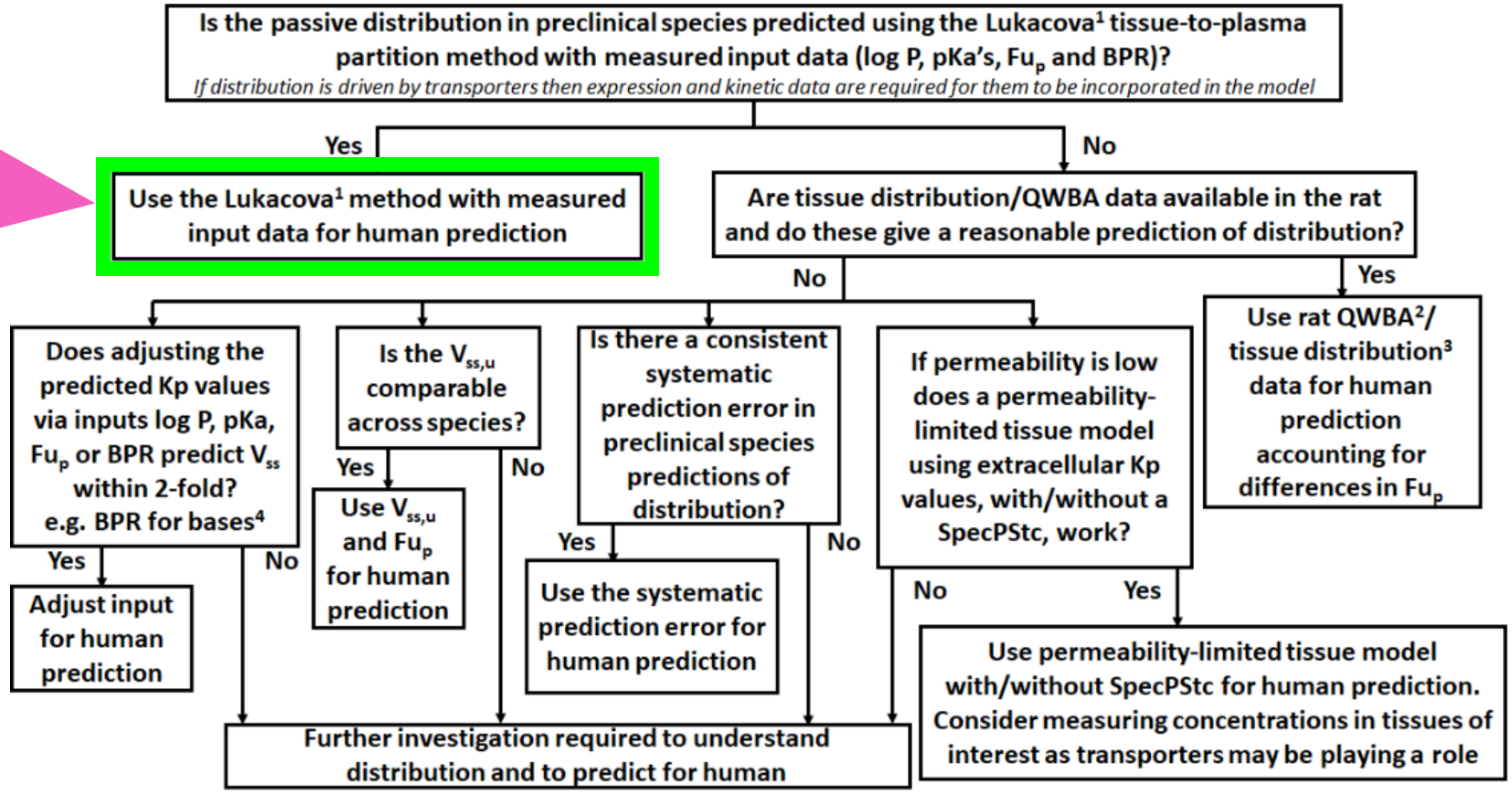
- Physchem = neutral and highly lipophilic (clogP >5)
- Plasma free fraction (<1 %) and aqueous solubility (<1 µg/mL) too low for accurate quantification
  - Difficult to verify an *In Vitro In Vivo* Extrapolation
- Preclinical *in vitro* and *in vivo* pharmacology promising
  - Extrapolation of pharmacokinetics was conducted to estimate a clinical dose

Drug data

Parameter	Value
clogP	5.2
Ionisation type (pKa)	Neutral
Fu_P (%)	< 0.1 in all species
Blood/plasma ratio	Human: 0.64 Rat: 0.83
Clearance mechanism (method)	Metabolic (in-vitro data)
Human Peff (cm/s × 10−4)	1.8 scaled from PAMPA
Solubility (µg/mL)	Aqueous solubility < 1

Distribution

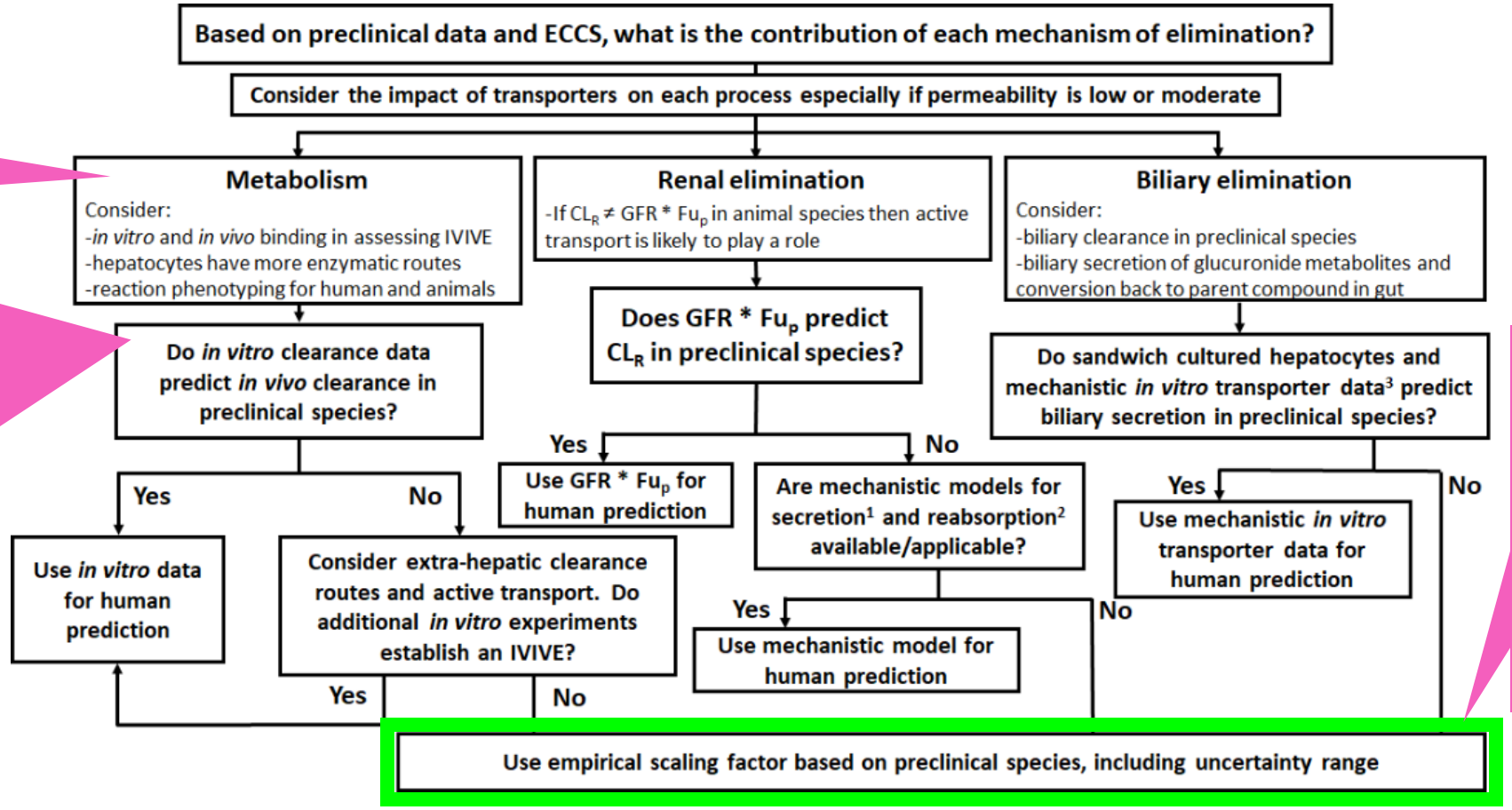
Predicted volumes using the Lukacova method based on the physicochemical properties and assuming a Fup of 0.1% for all species, were in reasonable agreement with the observed data



Metabolism & Elimination

Metabolically cleared based on *in vitro* data

Scaling of *in vitro* data to predict clearance should account for differences in binding *in vitro* and *in vivo*, but binding could not be measured. Assuming that *in vitro* free fraction was equivalent to Fup resulted in a large overprediction of clearance in the rat

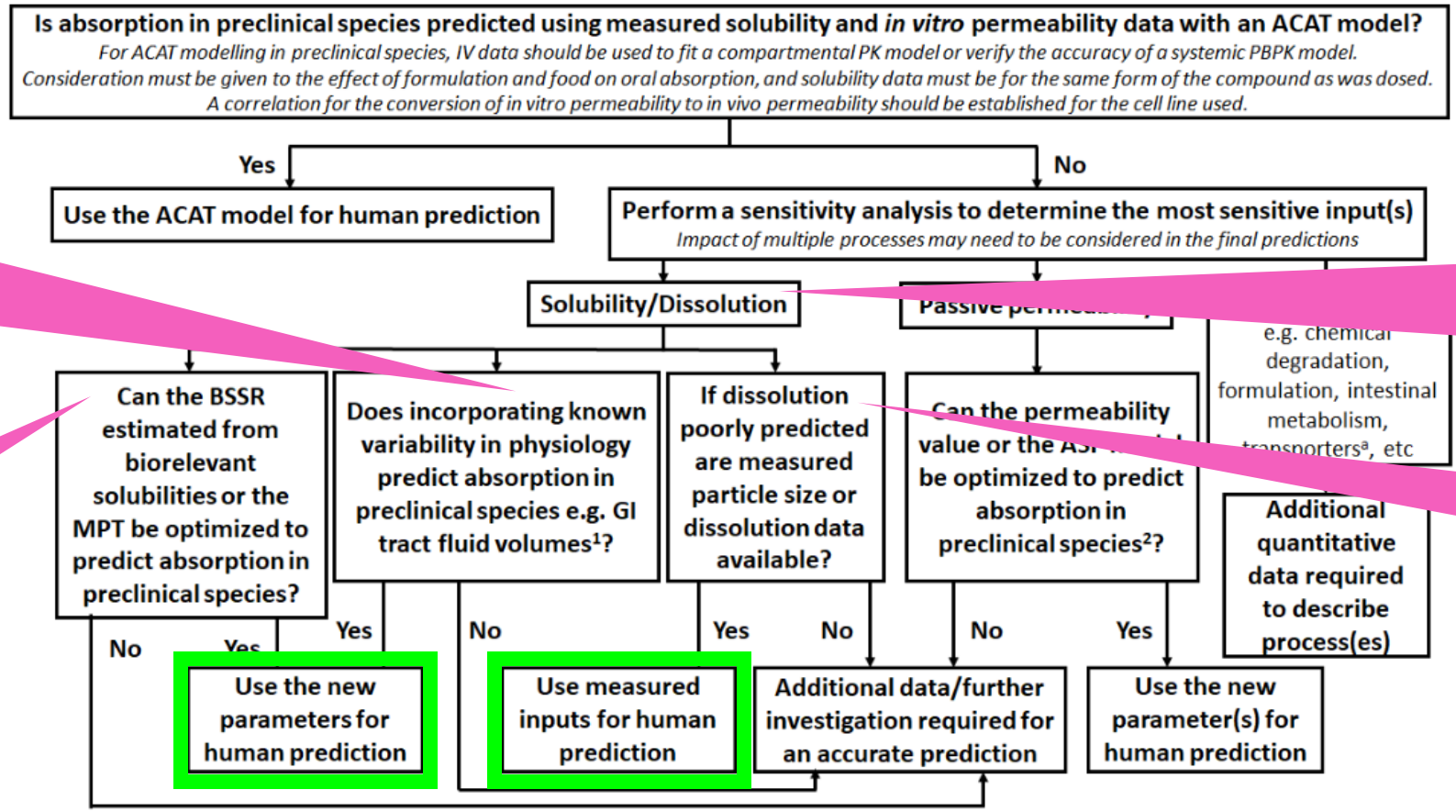


Human clearance was predicted using an empirical scaling factor derived from the rat which was verified by scaling of hepatocyte intrinsic clearances measured in dog and monkey

Oral absorption

*Physiological model parameter changes are not recommended best practice, but there is considerable uncertainty and ongoing debate over the relevant parameterization of intestinal water volumes!

- Challenging to predict oral absorption due to low solubility
- Due to predicted food effect, the first clinical study was conducted in the fed state



Percentage water in small intestine and colon compartments reduced from 40 & 10% to 10 & 0.1% respectively*

Solubility enhanced in biorelevant media

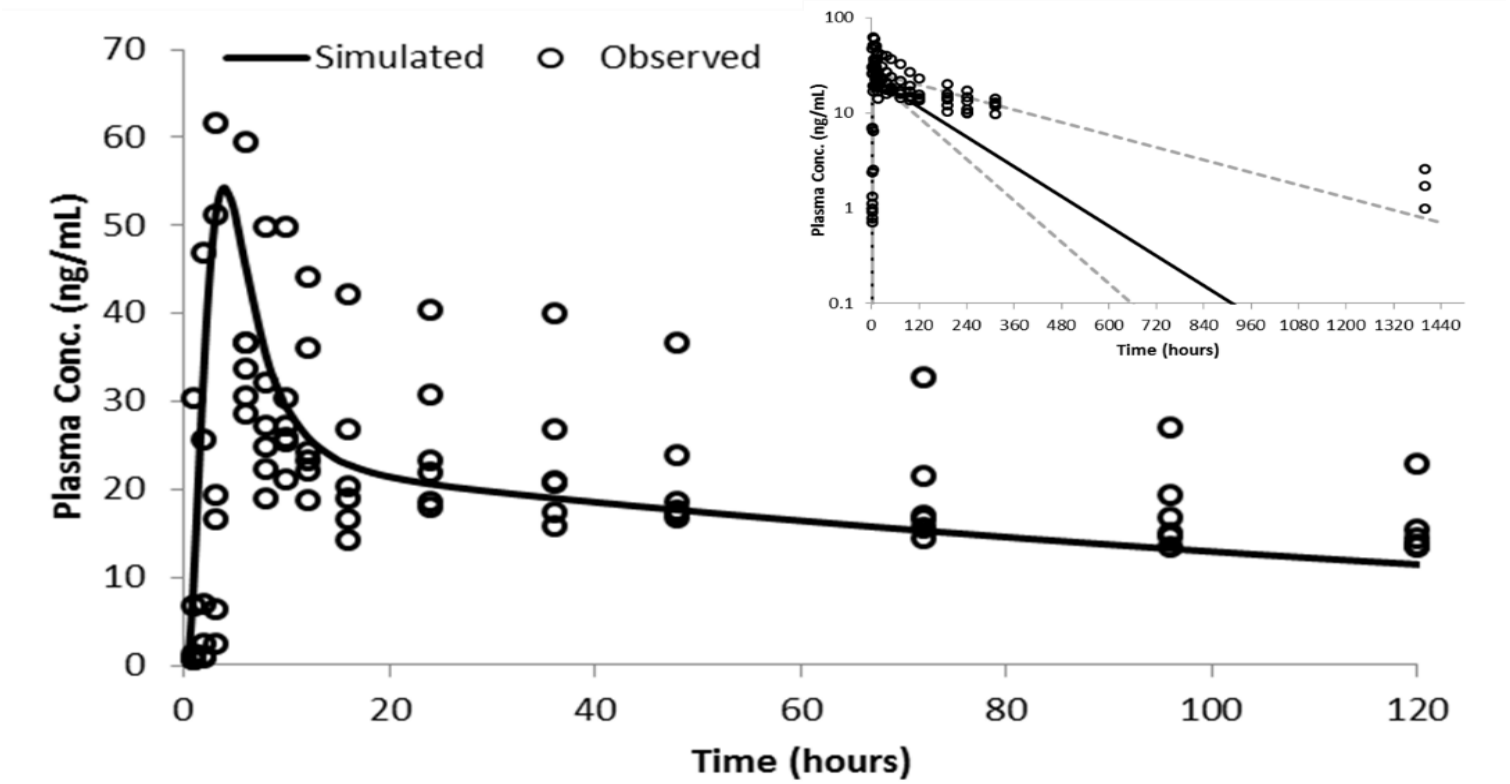
Preclinical data showed decreasing bioavailability with increasing dose with an influence of formulation and feeding status

Particle size: 1µm for nano-suspension & 80µm for tablets

Accuracy of predictions

Despite challenging properties, the pharmacokinetics prediction was good

- ✓ C_{max}
- ✓ V_{ss}
- ✓ **Bioavailability**



Greater than 2-fold under-prediction of AUC and $t_{1/2}$ longer than expected, but a later intravenous microdose study confirmed good predictions of bioavailability and V_{ss}

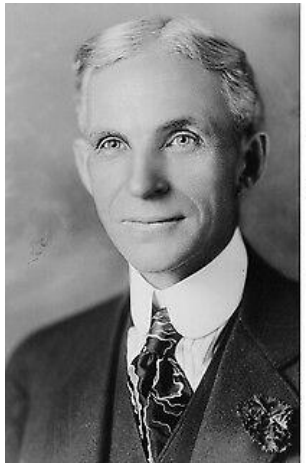
Learning gained

Never stop learning, because PBPK never stops teaching

Systemic clearance was at the lower end of the predicted range and **consideration of uncertainty** in clearance would have avoided a protocol amendment to adjust sampling times

Take home messages

- PBPK models are complex and combine systems physiology and drug specific input data
- Verification of PBPK models in preclinical R&D assesses whether the combination works for a specific drug
- Be realistic with your expectations and learn from poor predictions



"Failure is simply an opportunity to begin again, this time more intelligently."

Henry Ford

Acknowledgments

- Co-authors of the F.I.H PBPK strategy manuscript:
  - Neil Parrott (Roche)
  - Micaela Reddy (Pfizer)
  - Viera Lukacova (Simulations Plus)
  - Aki Heikkinen (Admescope)

Questions

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