SimulationsPlus

Unlocking the Power of PBPK Modeling: PBPK for First-in-Human and Beyond

March 20, 2024

Outline

- Proof PBPK Works for FIH PK Predictions
- Regulatory Perspective
- Breaking Down the Components of a PBPK Model
- Uncertainty and Sensitivity
- Model Applications

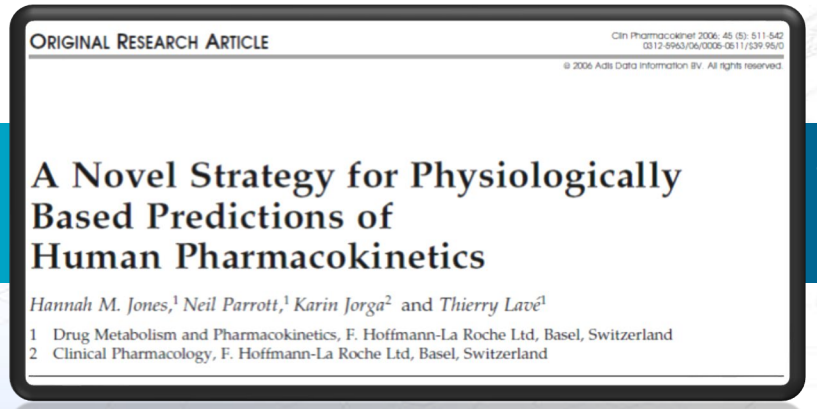
Considerations

- **Use everything that you know, but keep the model as simple as possible**
  - Aim to use PBPK not empirical modelling
  - Combine compound specific data with physiology as they are intimately interconnected and explicable only by reference to the whole
- **Preclinical verification can increase the accuracy of the human prediction but will always lead to learning**

Considerations

- **Always include uncertainty**
  - Never give single point estimates
- **Be realistic with your expectations**
  - A successful prediction gets the category right or within 2-fold, but not necessarily matching values exactly
- **Sensitivity analysis and model application can inform future decisions**
  - Apply model to gain insight into potential development questions

Proof PBPK Works for FIH PK Predictions



ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2006; 45 (5): 511-542
0312-5963/06/0005-0511/$39.95/0

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A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics

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

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

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

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DRUG METABOLISM AND DISPOSITION
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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

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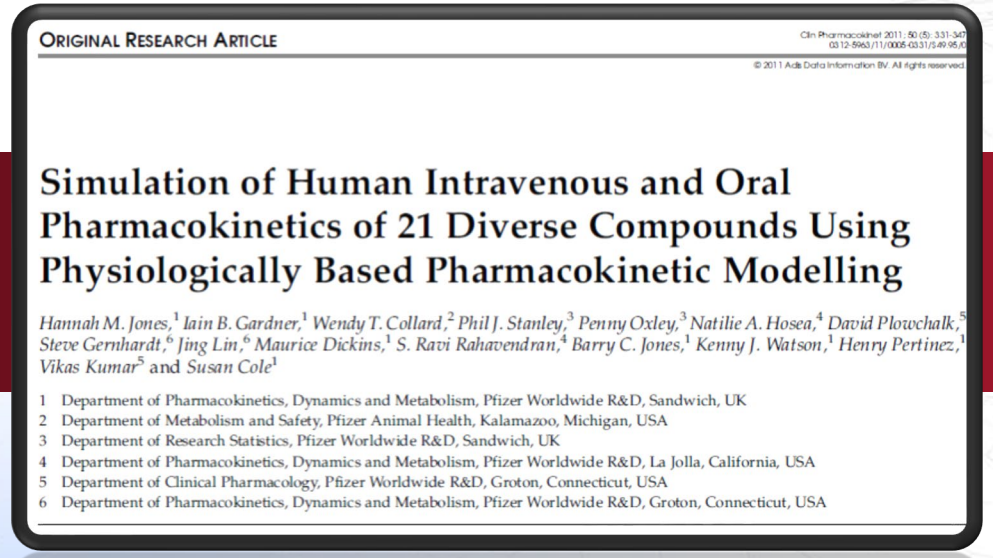
Received March 5, 2007; accepted July 3, 2007

Proof PBPK Works for FIH PK Predictions



ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2011; 50 (5): 331-347
0312-5963/11/0005-0331/$49.95/0

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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] Natilie A. Hosea,[4] David Plowchalk,[5] Steve Gernhardt,[6] Jing Lin,[6] Maurice Dickins,[1] S. Ravi Rahavendran,[4] Barry C. Jones,[1] Kenny J. Watson,[1] Henry Pertinez,[1] Vikas Kumar[5] and Susan Cole[1]

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"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."

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

RESEARCH ARTICLE – *Drug Discovery-Development Interface*

Prospective Predictions of Human Pharmacokinetics for Eighteen Compounds

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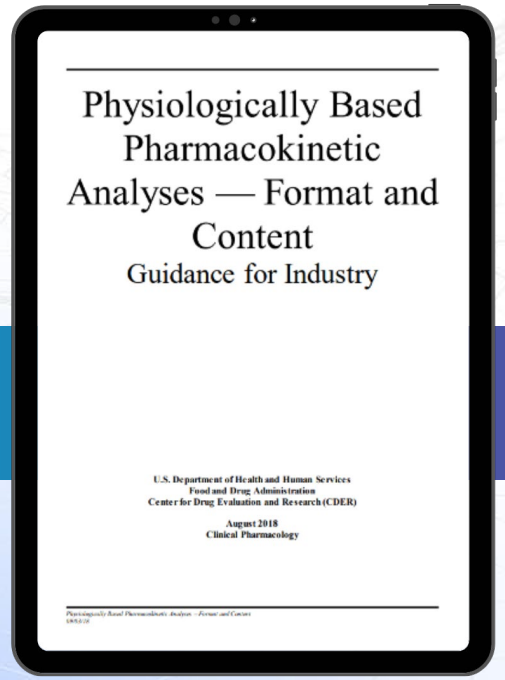
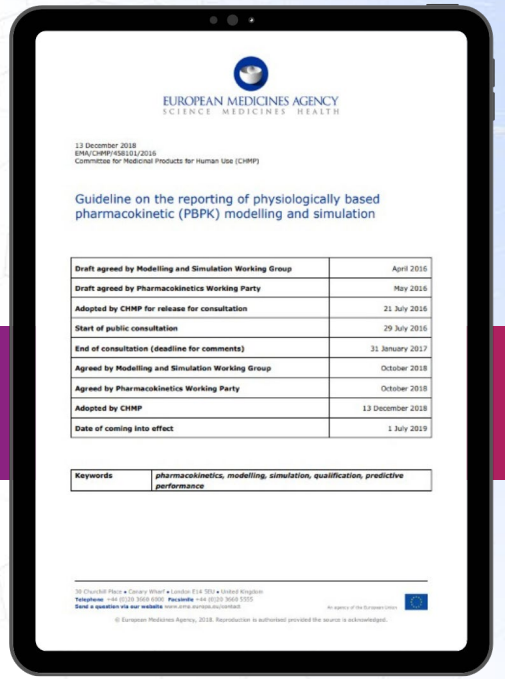
Regulatory Guidance for PBPK Modelling

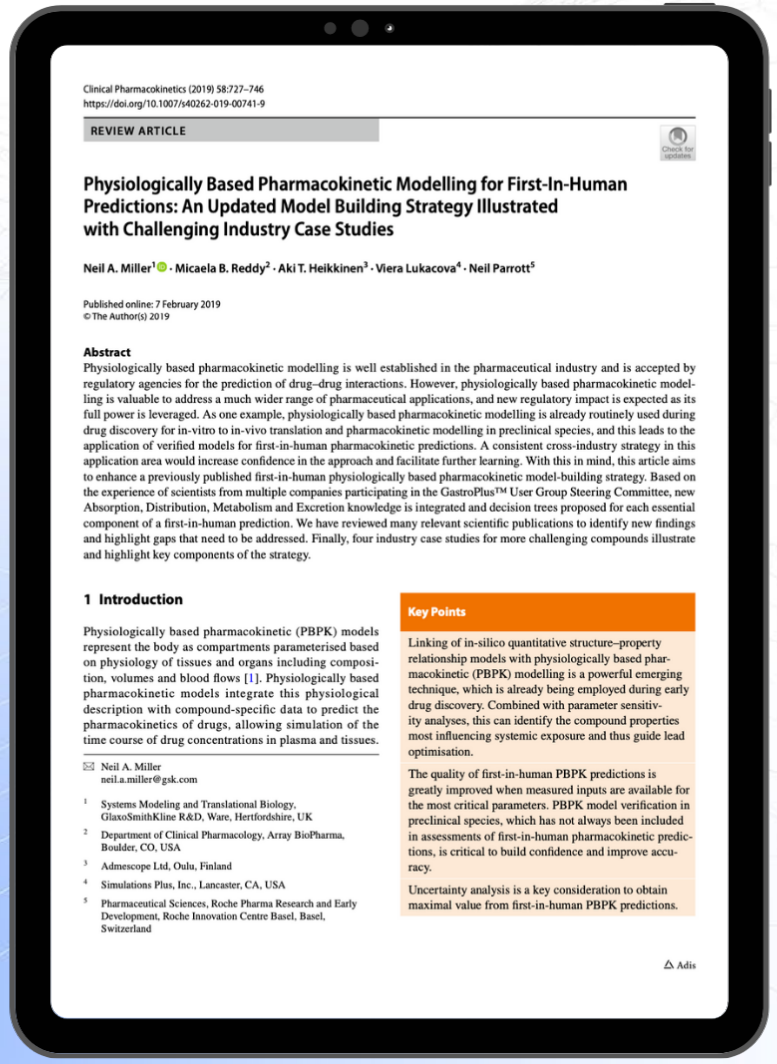




"Primarily for drug developers, FIH prediction using PBPK is important for decision-making and allows additional learning of the molecule and coping with situations when other methods may not be adequate."

"PBPK modelling is a state-of-the-art modelling tool for assessing an appropriate starting dose for healthy volunteers.[…] The methods used and calculations on how doses and estimated exposure levels are determined, including methods for modelling such as PBPK modelling, should be included in the protocol and may be summarised in the investigator's brochure"

An Industry Defined FIH PBPK Strategy



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]

Published online: 7 February 2019

Abstract
Physiologically based pharmacokinetic modelling is well established in the pharmaceutical industry and is accepted by regulatory agencies for the prediction of drug–drug interactions. However, physiologically based pharmacokinetic modelling is valuable to address a much wider range of pharmaceutical applications, and new regulatory impact is expected as its full power is leveraged. As one example, physiologically based pharmacokinetic modelling is already routinely used during drug discovery for in-vitro to in-vivo translation and pharmacokinetic modelling in preclinical species, and this leads to the application of verified models for first-in-human pharmacokinetic predictions. A consistent cross-industry strategy in this application area would increase confidence in the approach and facilitate further learning. With this in mind, this article aims to enhance a previously published first-in-human physiologically based pharmacokinetic model-building strategy. Based on the experience of scientists from multiple companies participating in the GastroPlus™ User Group Steering Committee, new Absorption, Distribution, Metabolism and Excretion knowledge is integrated and decision trees proposed for each essential component of a first-in-human prediction. We have reviewed many relevant scientific publications to identify new findings and highlight gaps that need to be addressed. Finally, four industry case studies for more challenging compounds illustrate and highlight key components of the strategy.

1 Introduction

Physiologically based pharmacokinetic (PBPK) models represent the body as compartments parameterised based on physiology of tissues and organs including composition, volumes and blood flows [1]. Physiologically based pharmacokinetic models integrate this physiological description with compound-specific data to predict the pharmacokinetics of drugs, allowing simulation of the time course of drug concentrations in plasma and tissues.

Key Points

Linking of in-silico quantitative structure–property relationship models with physiologically based pharmacokinetic (PBPK) modelling is a powerful emerging technique, which is already being employed during early drug discovery. Combined with parameter sensitivity analyses, this can identify the compound properties most influencing systemic exposure and thus guide lead optimisation.

The quality of first-in-human PBPK predictions is greatly improved when measured inputs are available for the most critical parameters. PBPK model verification in preclinical species, which has not always been included in assessments of first-in-human pharmacokinetic predictions, is critical to build confidence and improve accuracy.

Uncertainty analysis is a key consideration to obtain maximal value from first-in-human PBPK predictions.

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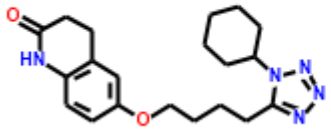
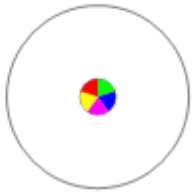
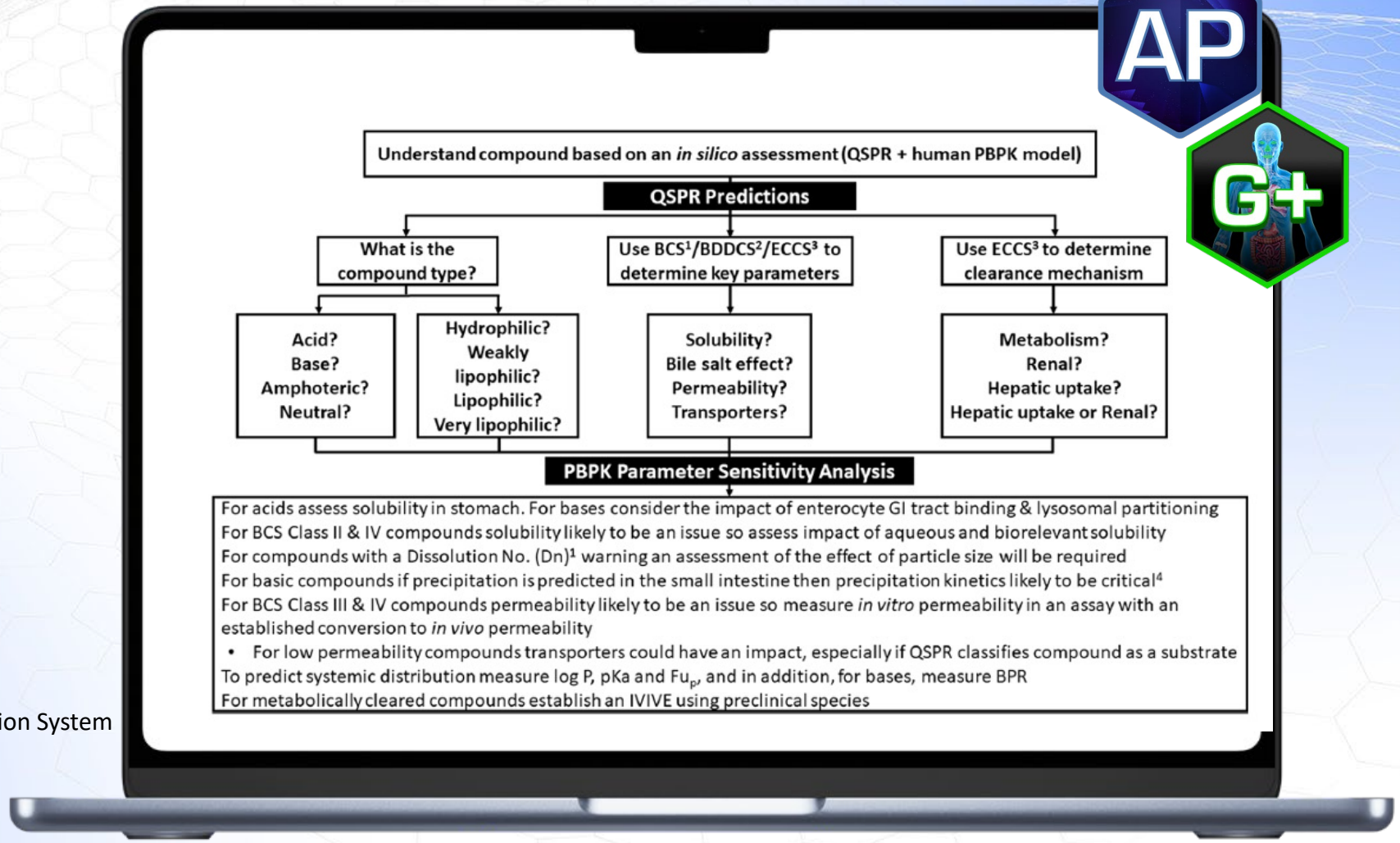
Flow diagrams for each essential component of a FIH prediction using PBPK modelling

Use Everything You Know

- **FIH Simulator includes the major preclinical species to enable you to move seamlessly from mouse, rat, dog, minipig, rabbit, cyno through to human in one platform**
  - The overall risk profile can be assessed in ADMET Predictor
  - Inputs without measured data can be predicted using ADMET Predictor
  - NCA and compartmental analysis can be performed within the software
  - Measured or predicted metabolism data for individual enzymes can be incorporated which in turn allows an assessment of potential gut metabolism and phenotypic variability

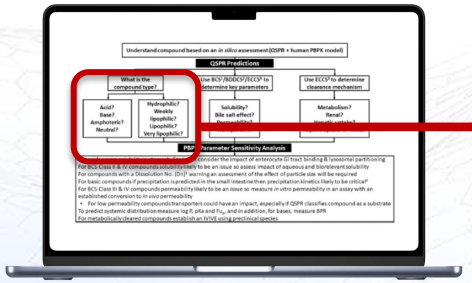
Structure	Identifier	*Risks*	*Tox*	ADMET_Risk	ADMET_Code	ECCS_Class	Absn_Risk	Absn_Code	RuleOf5	RuleOf5_Code	CYP_Risk	CYP_Code
	Cilostazol			1.000	3A4	Class_2	0.000		0.000		1.000	3A4

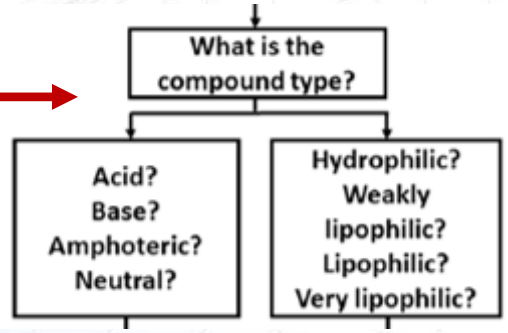
Use Everything You Know: Start with QSPR + PBPK

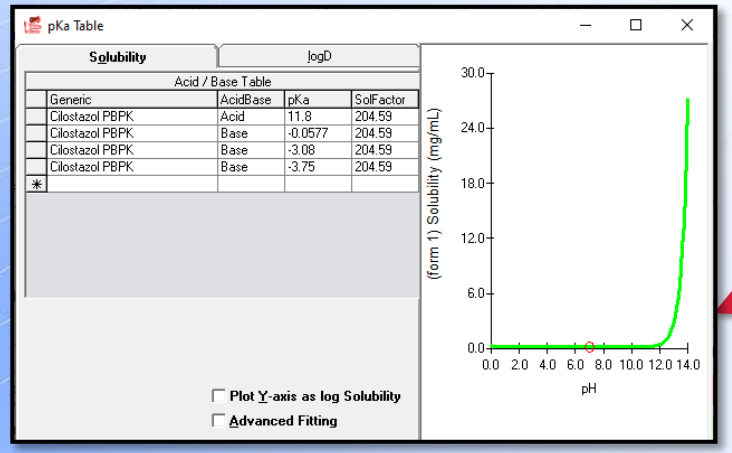


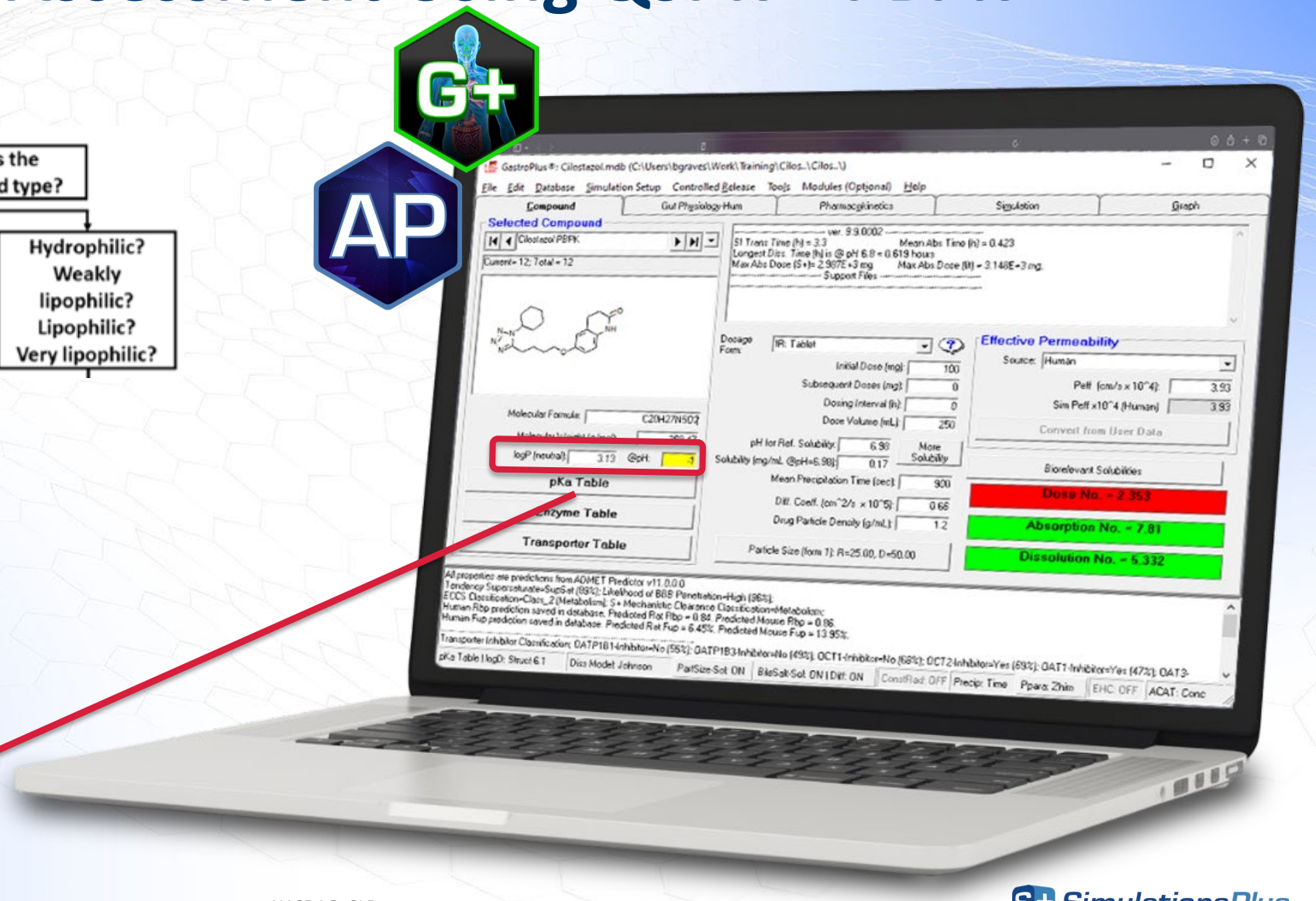
- BDDCS – Biopharmaceutics Drug Disposition Classification System
- ECCS – Extended Clearance Classification System
- QSPR – Quantitative Structure-Property Relationship
- BCS – Biopharmaceutic Classification System

Use Everything You Know: Compound Assessment Using QSPR + PBPK

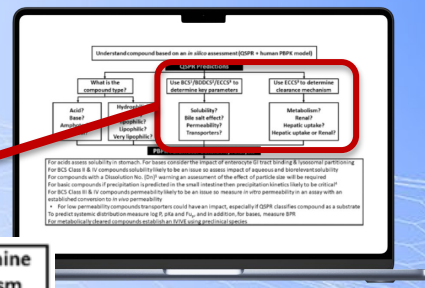








Use Everything You Know: Critical Thinking Using QSPR + PBPK



Use BCS[1]/BDDCS[2]/ECCS[3] to determine key parameters

Use ECCS[3] to determine clearance mechanism

Solubility?
Bile salt effect?
Permeability?
Transporters?

Metabolism?
Renal?
Hepatic uptake?
Hepatic uptake or Renal?

Cutoff between low and high permeability is 1.2cm/s x 10^4 based on metoprolol

Bile Salt Effect

- Adjust solubility for bile salt effect
- Adjust diff coeff for bile salt effect
- Solubilization Ratio (SR): 0 — Fit to In Vitro Data
- SR Exponent (N): 1 — Include N in fit
- Use theoretical solubilization ratio

Duodenal solubility at bile salt concentration 2.8mM will be 759.0 mg/mL for form 1

Biorelevant In Vitro Solubilities

Use the biorelevant solubilities of form 1

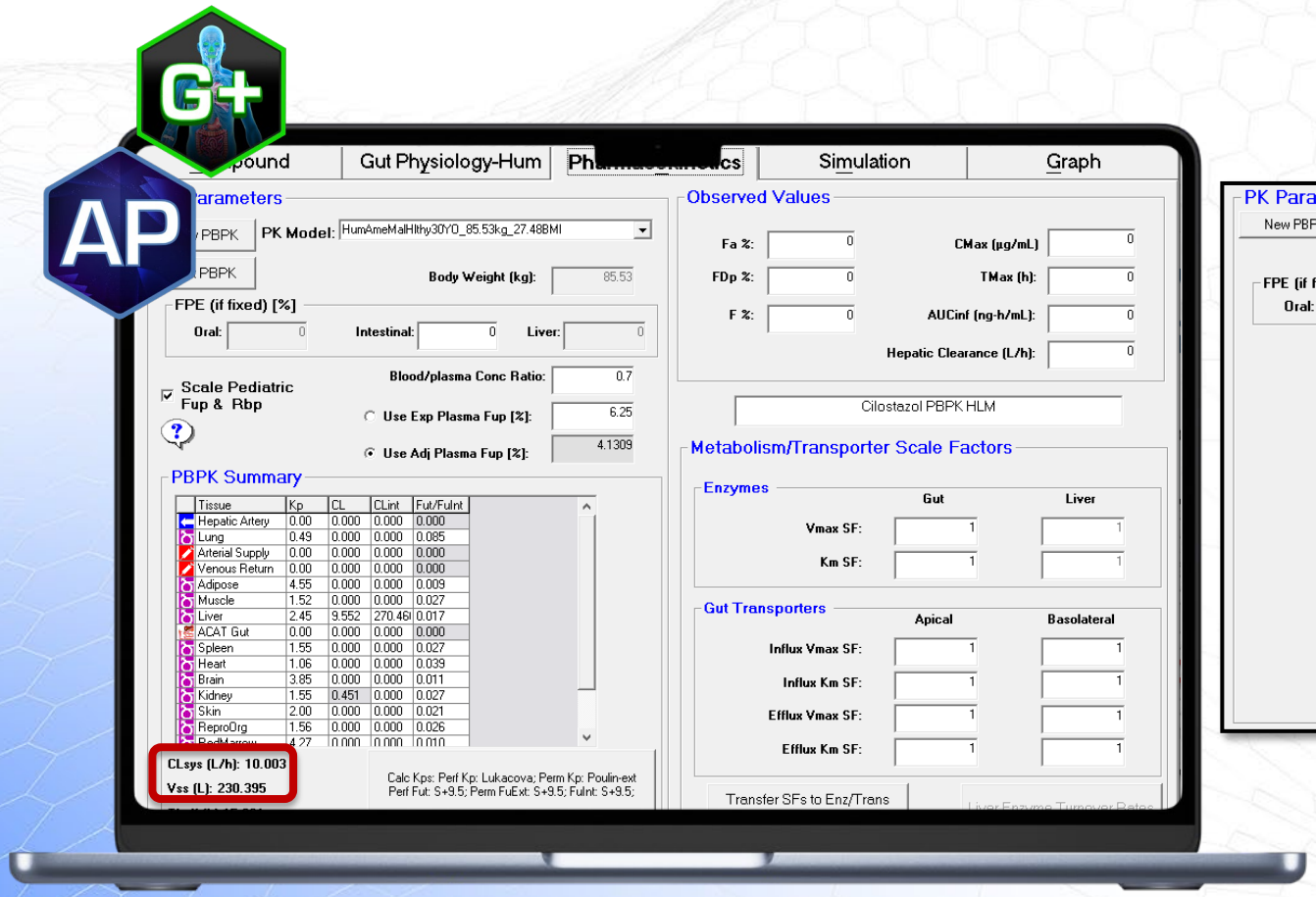
At least one of the FaSSIF, FeSSIF, or User solubilities must be specified to calculate solubilization ratio

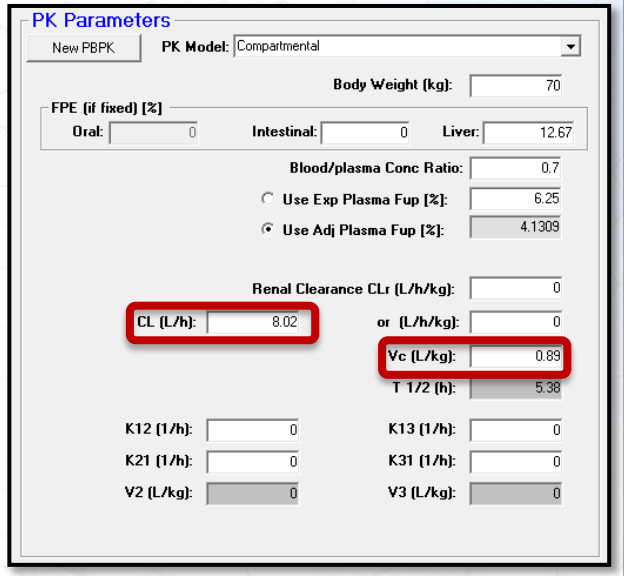
Enter 0 for values of biorelevant solubilites that are not available. Zero values are not used in SR calculation

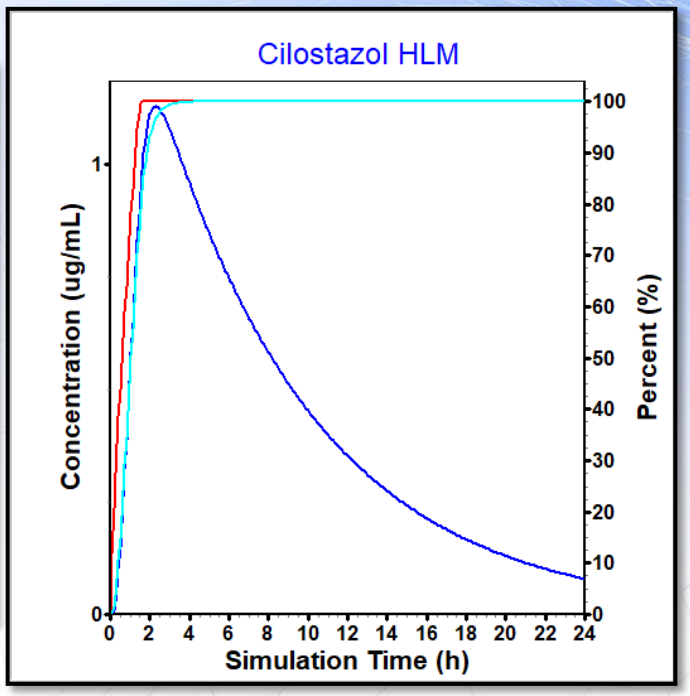
	SGF	FaSSIF	FeSSIF	FeSSIF V2	User
pH:	1.2	6.5	5	5.8	0
Bile Salt Conc (mM):	0	3	15	10	0
Exp. Sol. (mg/mL):	17.04	189.85	0	48.16	0
Calc. Sol. (mg/mL):		668.0		797.3	

ECCS, S+ Mechanistic Clearance Classification and transporter substrate predictions are in the notes

Use Everything You Know: Pragmatic Assessment Using QSPR + PBPK





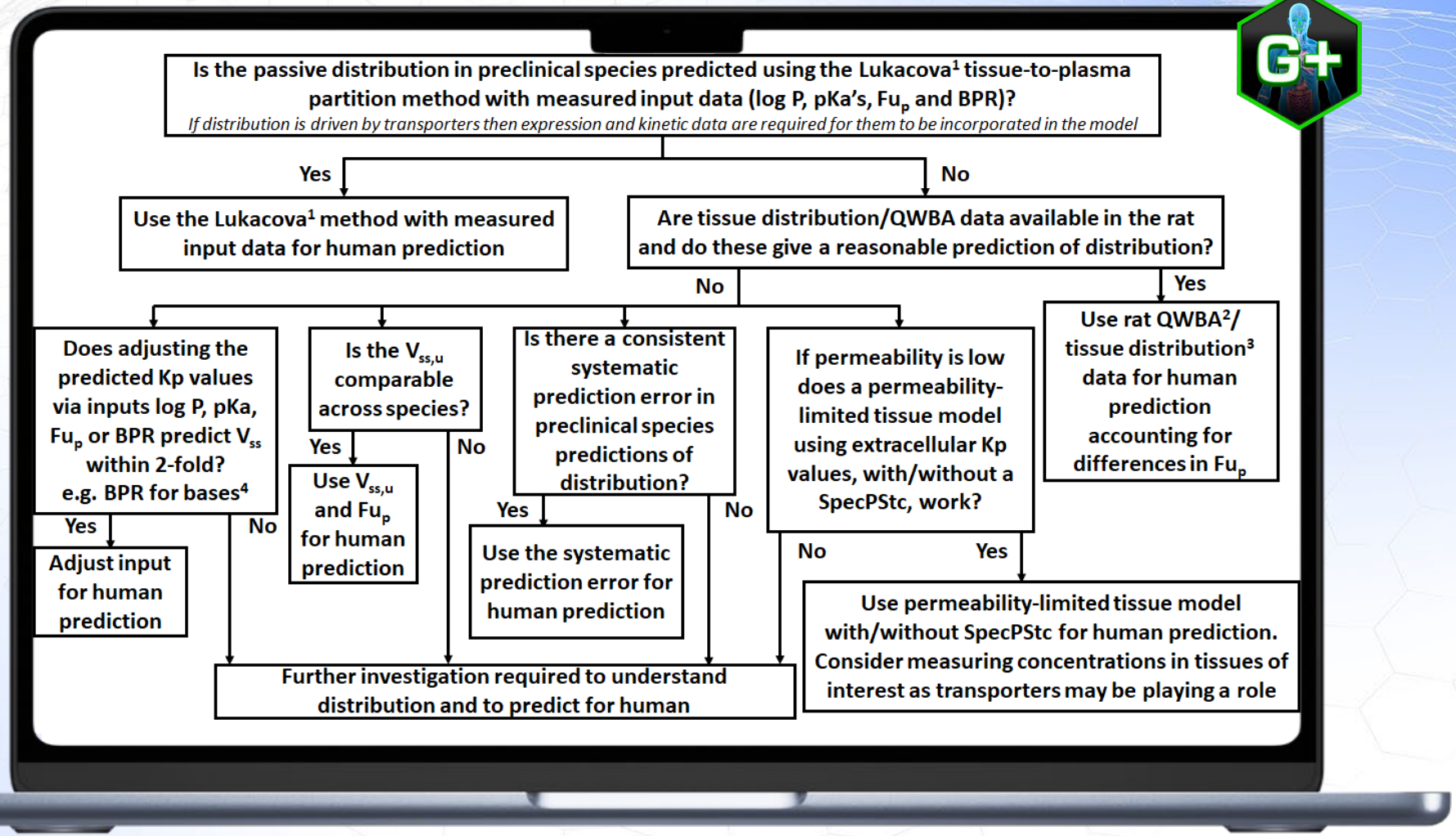


Blue – Plasma concentration
Red – Amount dissolved
Cyan – Amount absorbed

Multiple options to predict clearance: models for HLM, hepatocytes, enzyme kinetics

Preclinical Verification to Better Predict Human PK

Distribution



- 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.

Preclinical Verification: Assessing the Pieces of the Jigsaw Puzzle

FIH prediction for IV dosing of Tobramycin : Distribution

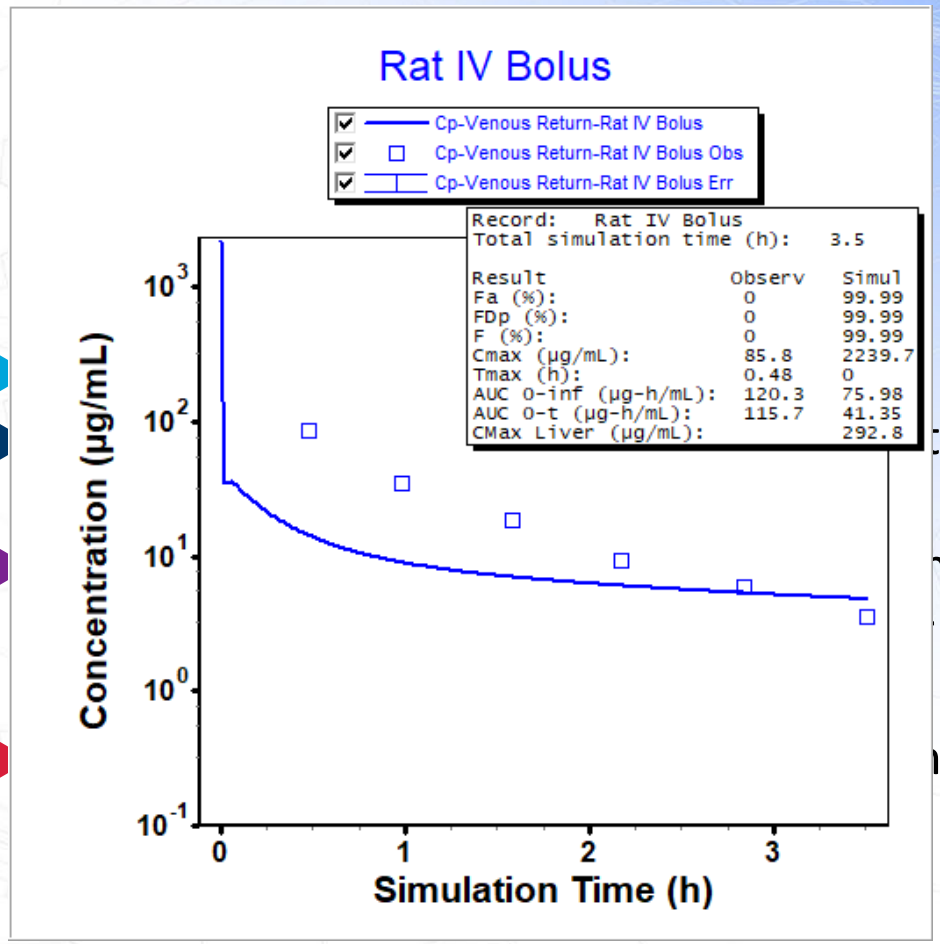
- Preclinical IV Cp vs Time profiles
- LogP/D
- pKa
- Fraction unbound in plasma (Fup)
- Blood to plasma ratio (RBP)

- Use the Lukacova Kp equation
- Input available measured data
- PBPK record per preclinical species
- PKPlus: calculate the NCA CL and V_{ss}
- Liver CL = NCA CL - CL_R

Preclinical Verification: Applying Critical Thinking

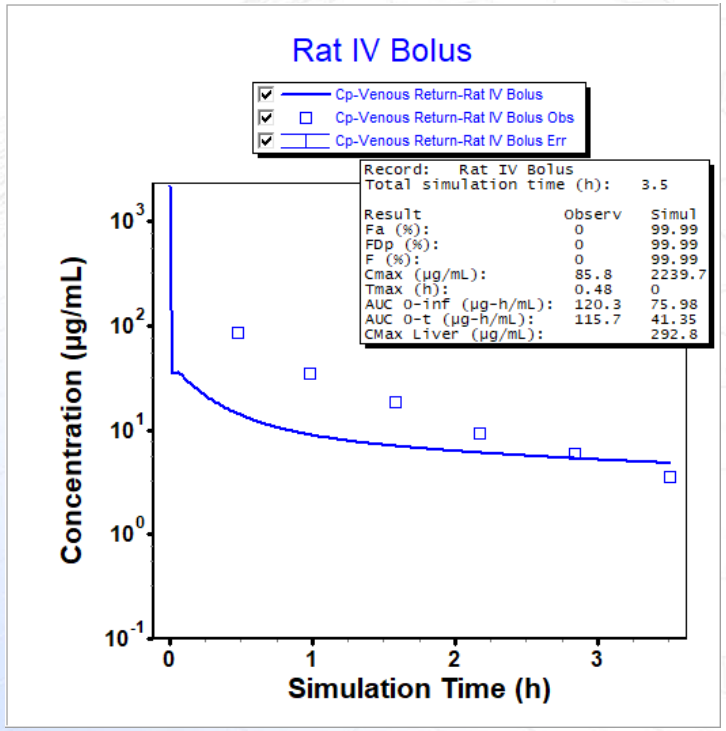
FIH prediction for IV dosing of Tobramycin : Distribution

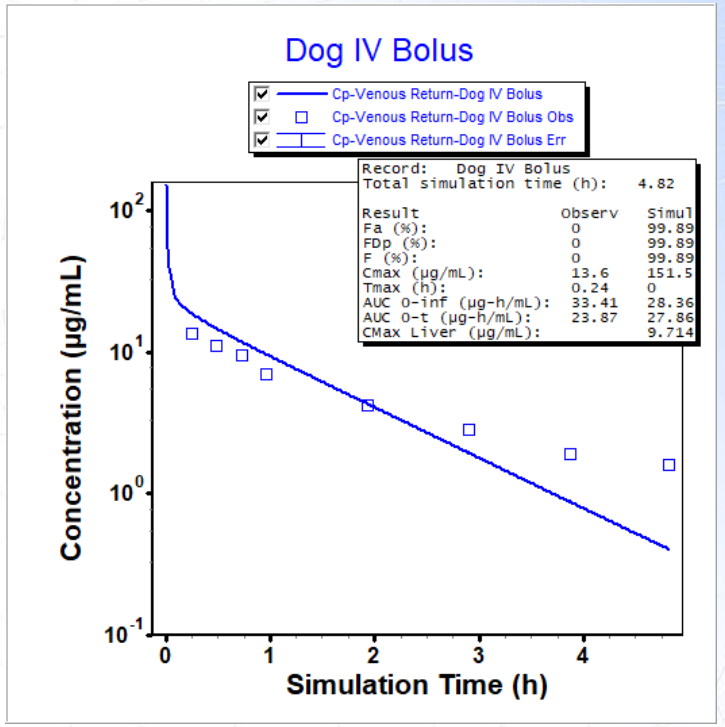
- Predicted Vss is too large causing a rapid distribution to tissues and a slow return to systemic circulation
- Knowing your compound can guide the modelling strategy
- Tobramycin is a low permeability compound so…



Preclinical Verification: Applying Critical Thinking

FIH prediction for IV dosing of Tobramycin : Distribution

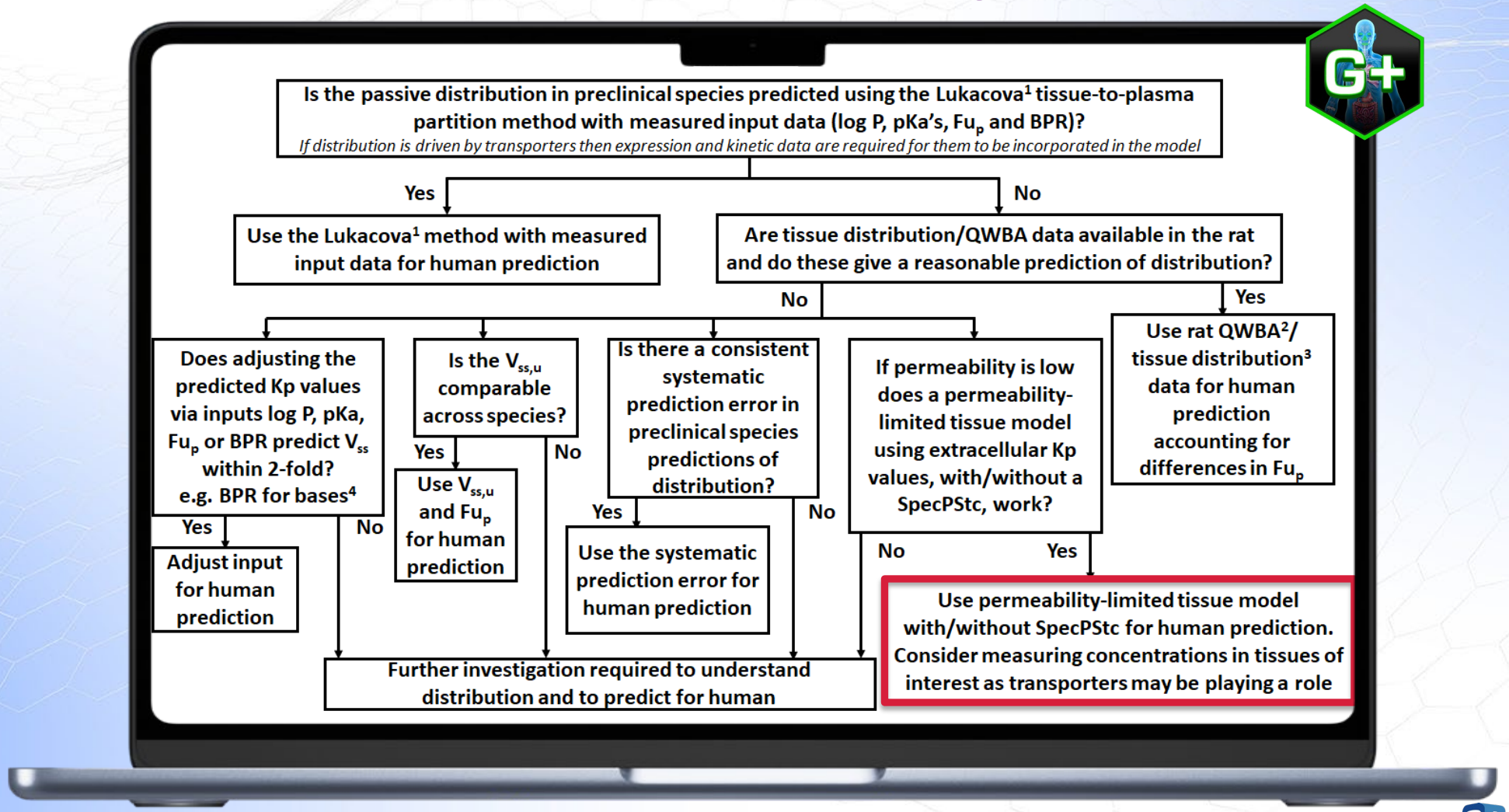




Species	Observed Vss	Predicted Vss	Pred/Obs
Rat	0.093 L	0.190 L	2.0
Dog	12.24 L	16.63 L	1.4

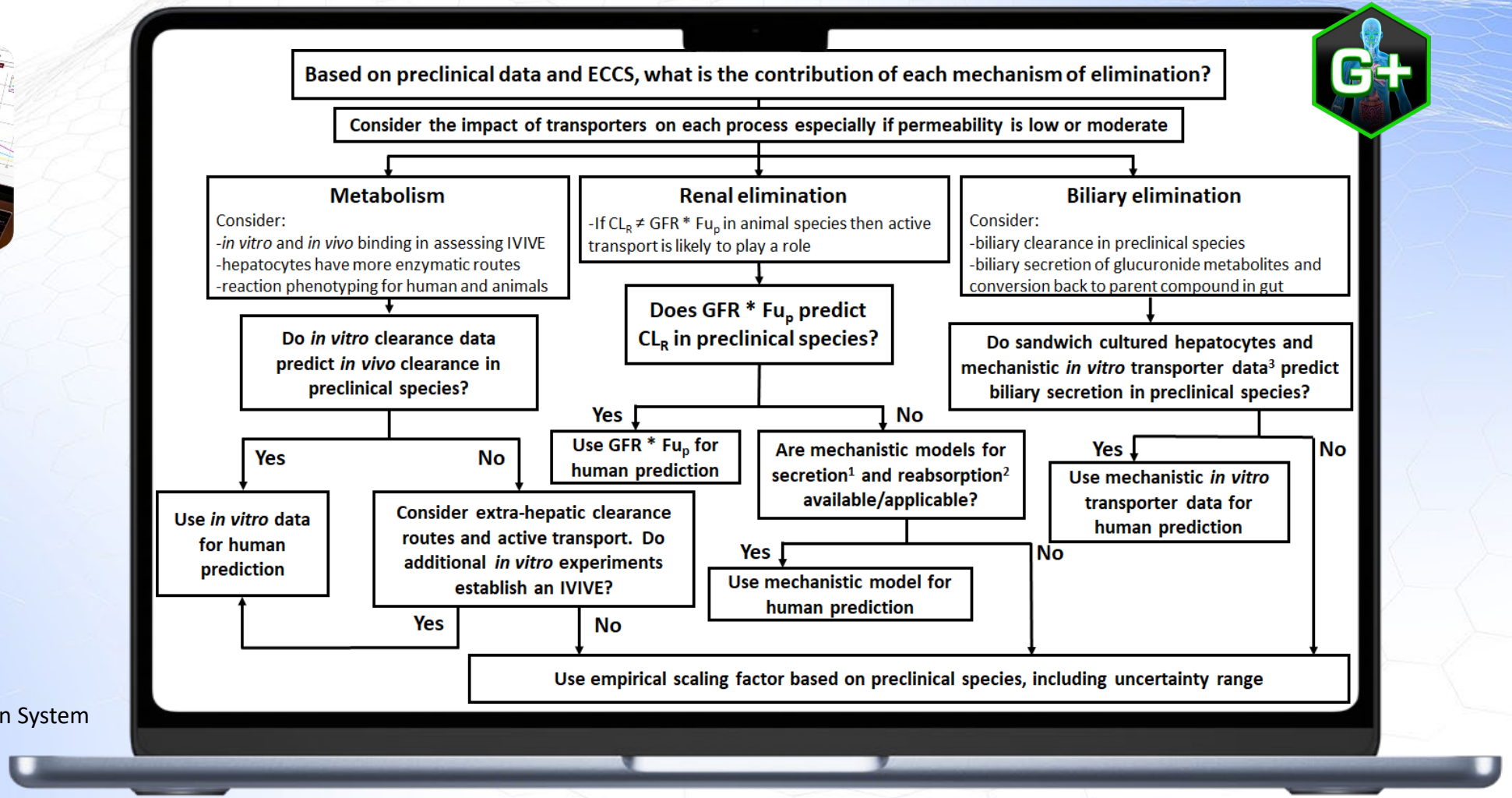
Preclinical Verification Defines Strategy for Human Prediction

Distribution -Tobramycin



Preclinical Verification to Better Predict Human PK

Metabolism and Elimination



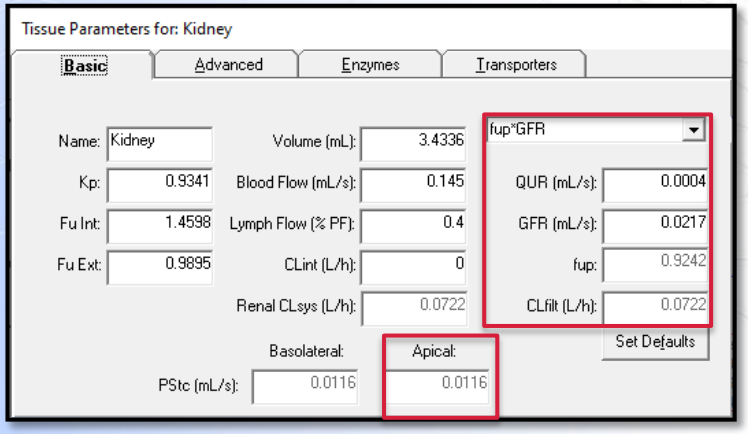
- CL_R renal clearance
- $CL_{R,u}$ unbound renal clearance
- ECCS Extended Clearance Classification System
- Fup fraction unbound in plasma
- GFR glomerular filtration rate
- IVIVE *in-vitro in-vivo* extrapolation.

Preclinical Verification:
Combining Measured Data with Predicted Properties

Metabolism and Elimination

- Renal clearance from IV studies
- Observed or in vitro biliary clearance data
- Microsomal, hepatocyte or enzyme kinetic data

- Validate CL_R prediction
- Adjust CL_R settings in the kidney tissue to account for active processes
- Parameterise and validate biliary clearance
- Use Metabolism and Transporter module to assess IVIVC



Preclinical Verification:
Combining Measured Data with Predicted Properties

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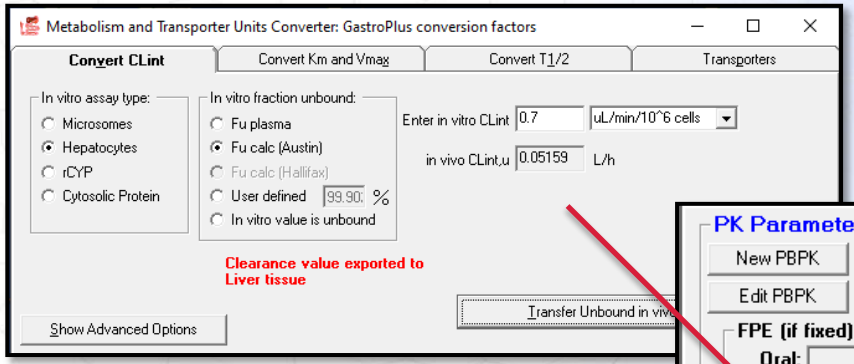
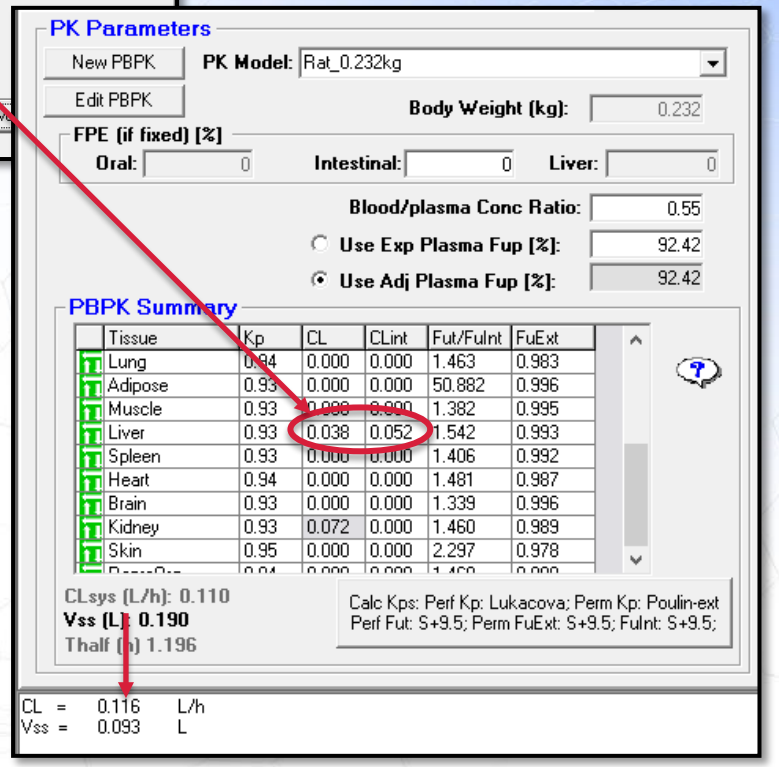
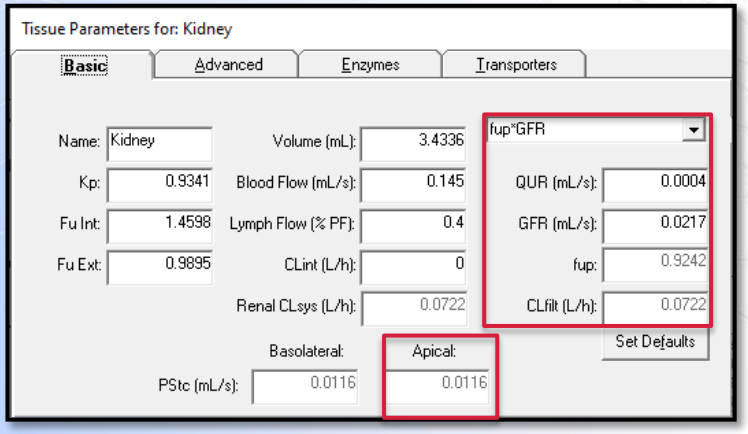
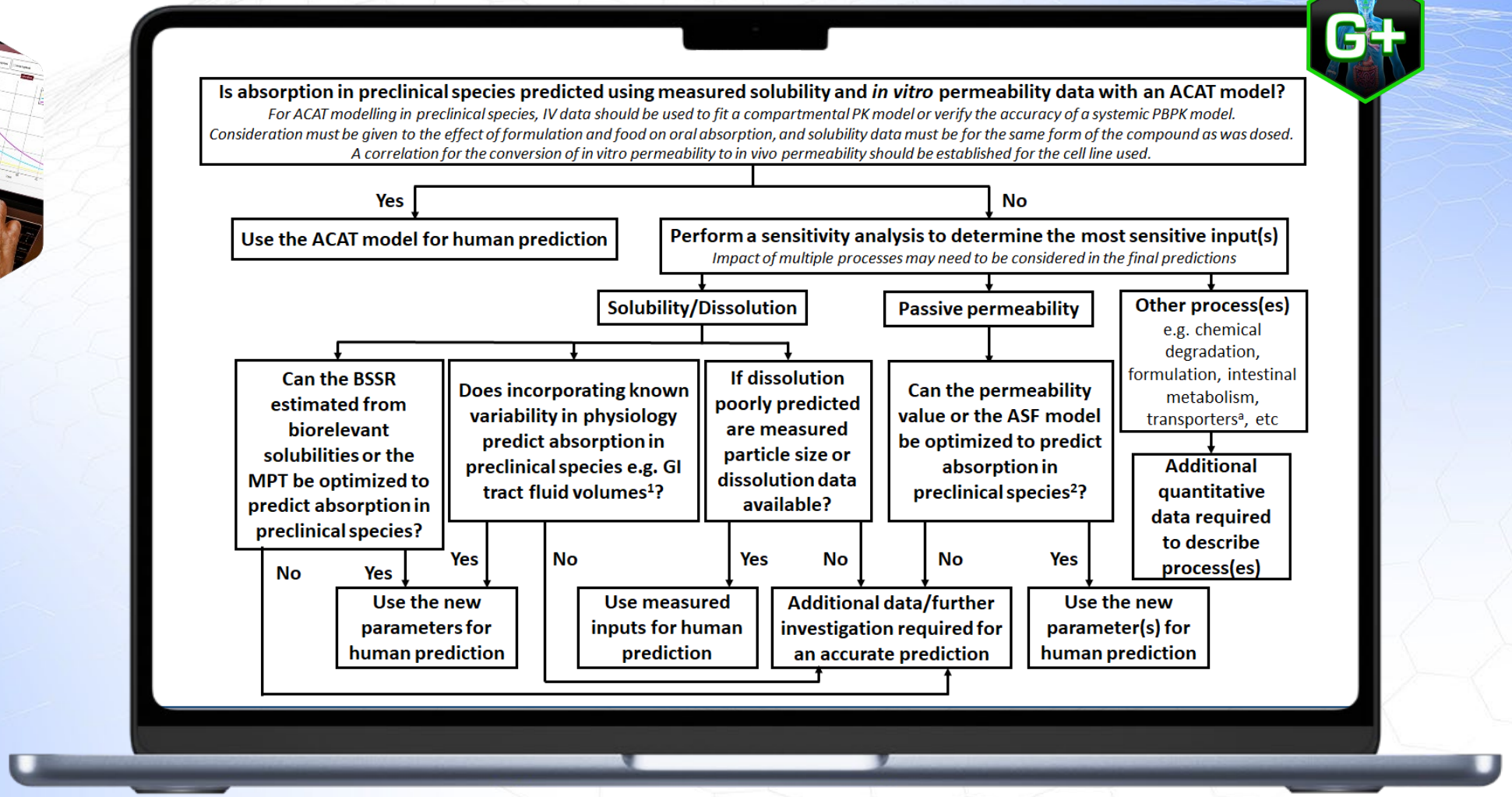






Preclinical Verification to Better Predict Human PK

Oral Absorption

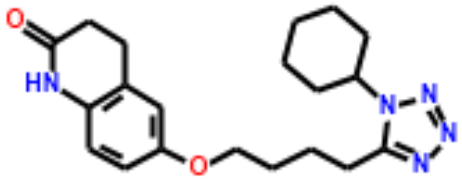


- ASF absorption scale factors
- BSSR bile salt solubilisation ratio
- MPT mean precipitation time
- Efflux transporters can be incorporated in GastroPlus models with a simple method (e.g. adjusting permeability based on preclinical observations or in-vitro data) to more complex methods (e.g. specifically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

Preclinical Verification: Building on the IV Model

FIH prediction for PO dosing of Cilostazol : Oral Absorption

- Moderately lipophilic
- Essentially neutral at physiological pH
- Low to moderate solubility
- Reasonable permeability
- Low bile salt effect
- Dog PO PK



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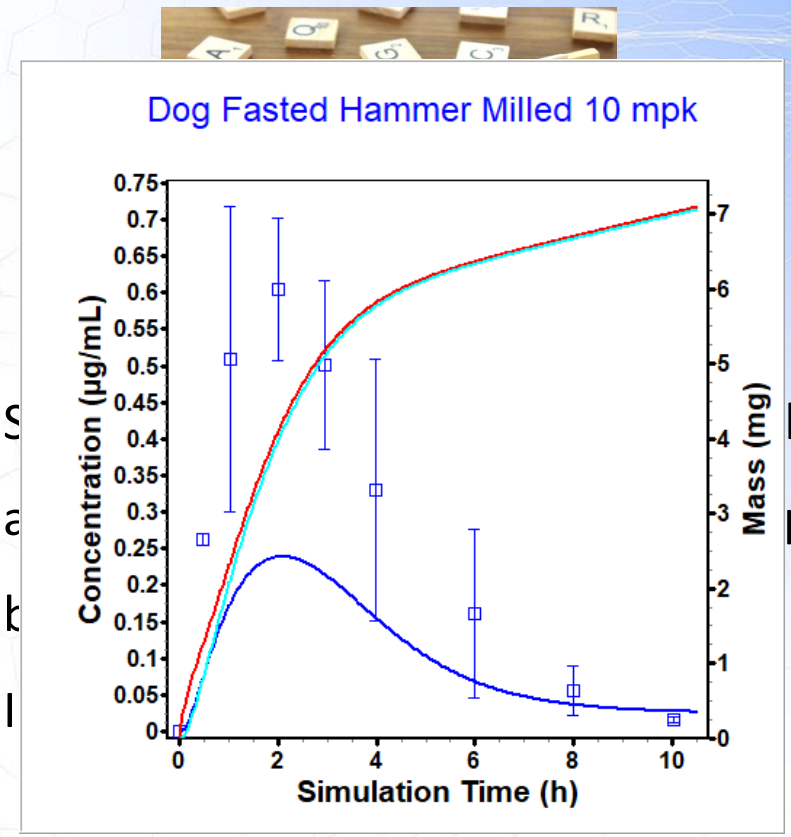
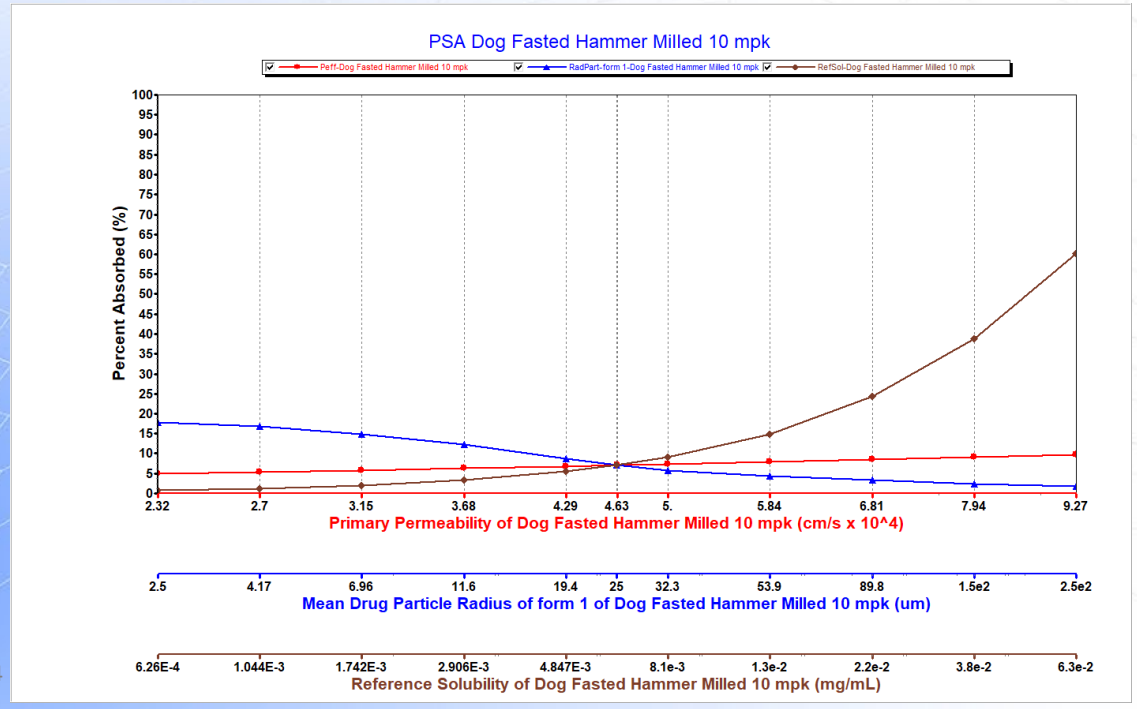


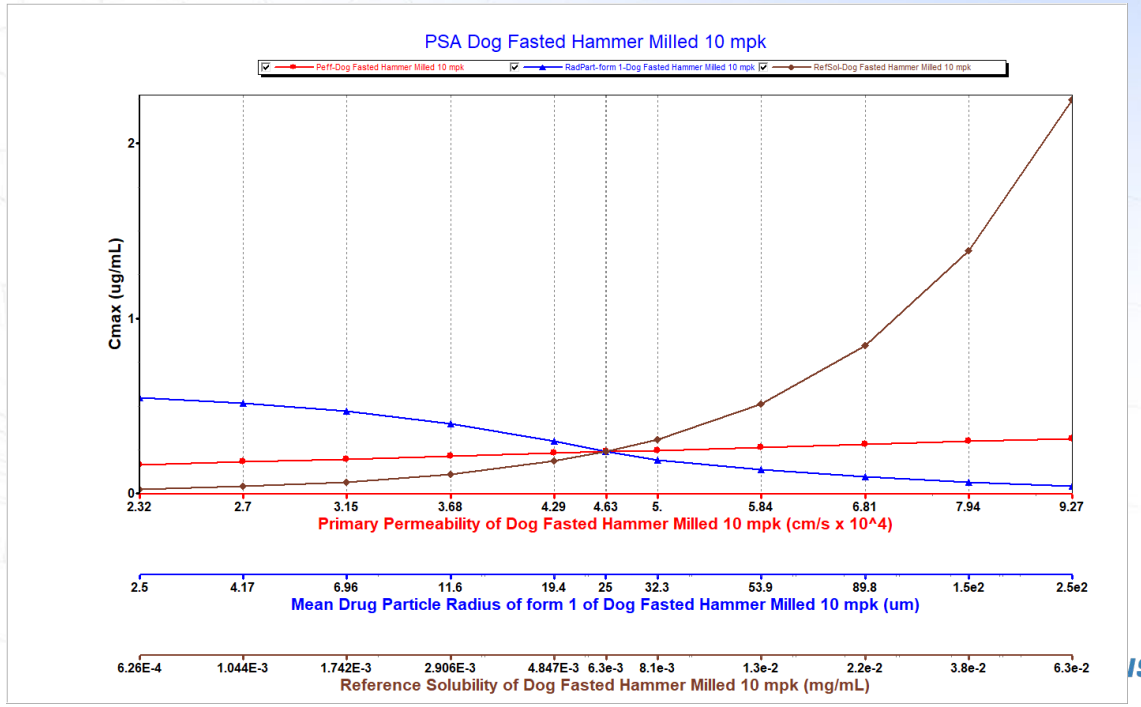
Blue – Plasma concentration
Red – Amount dissolved
Cyan – Amount absorbed

Preclinical Verification : Assessing the sensitive parameters

FIH prediction for PO dosing of Cilostazol : Oral Absorption

	Parameter	Lower Bound	Baseline Value	Upper Bound	Number of Test	Spacing of Param Values
▶	Primary Permeability of Dog Fasted Hammer Milled 10 mpk (cm/s x 10^4)	2.316	4.633	9.266	10	Logarithmic
	Mean Drug Particle Radius of form 1 of Dog Fasted Hammer Milled 10 mpk (um)	2.5	25	250	10	Logarithmic
	Reference Solubility of Dog Fasted Hammer Milled 10 mpk (mg/mL)	0.000626	0.00626	0.063	10	Logarithmic





Preclinical Verification : Additional measured data to enable prediction

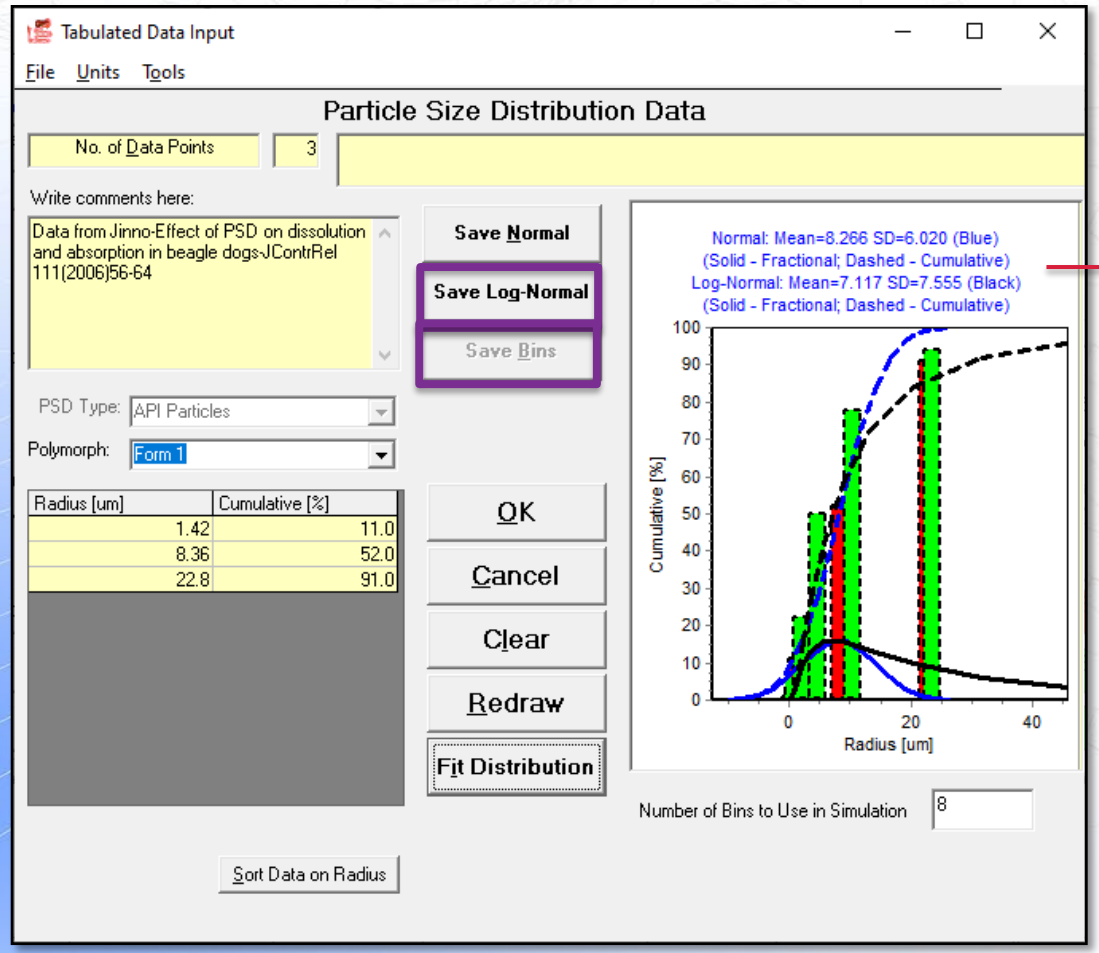
FIH prediction for PO dosing of Cilostazol : Oral Absorption

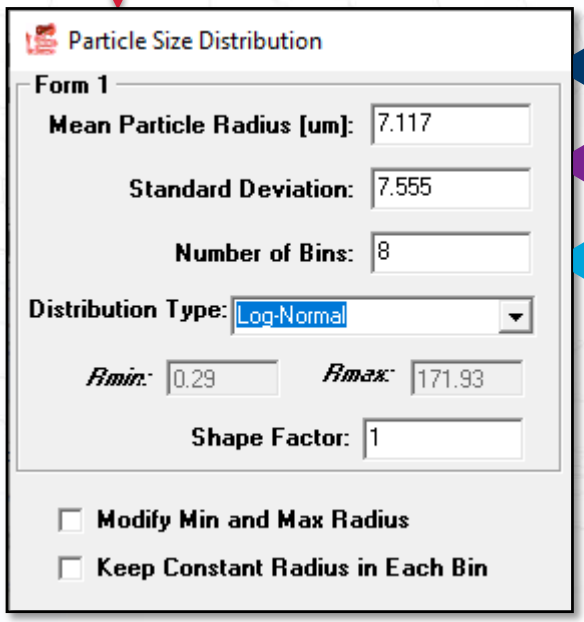
- Dissolution is the rate limiting step for absorption
- Solubility has been fitted to measured pKas
- Particle size data is available

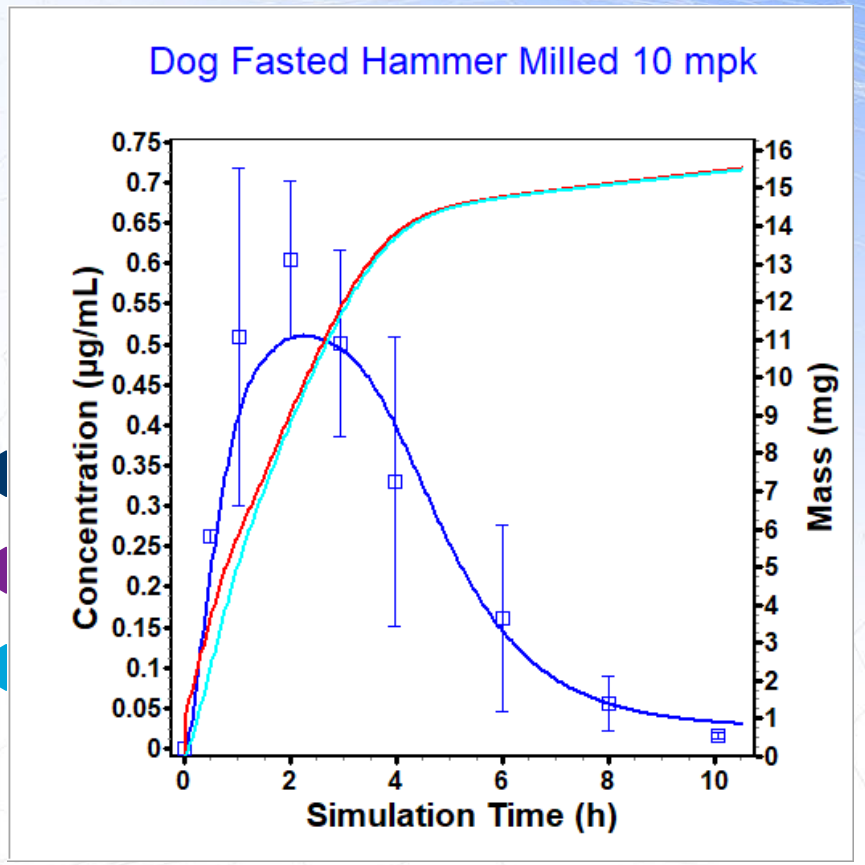
- Fit distribution to particle size data
- Apply to model
- Verify with other doses / species / formulations

Preclinical Verification : Additional measured data to enable prediction

FIH prediction for PO dosing of Cilostazol : Oral Absorption





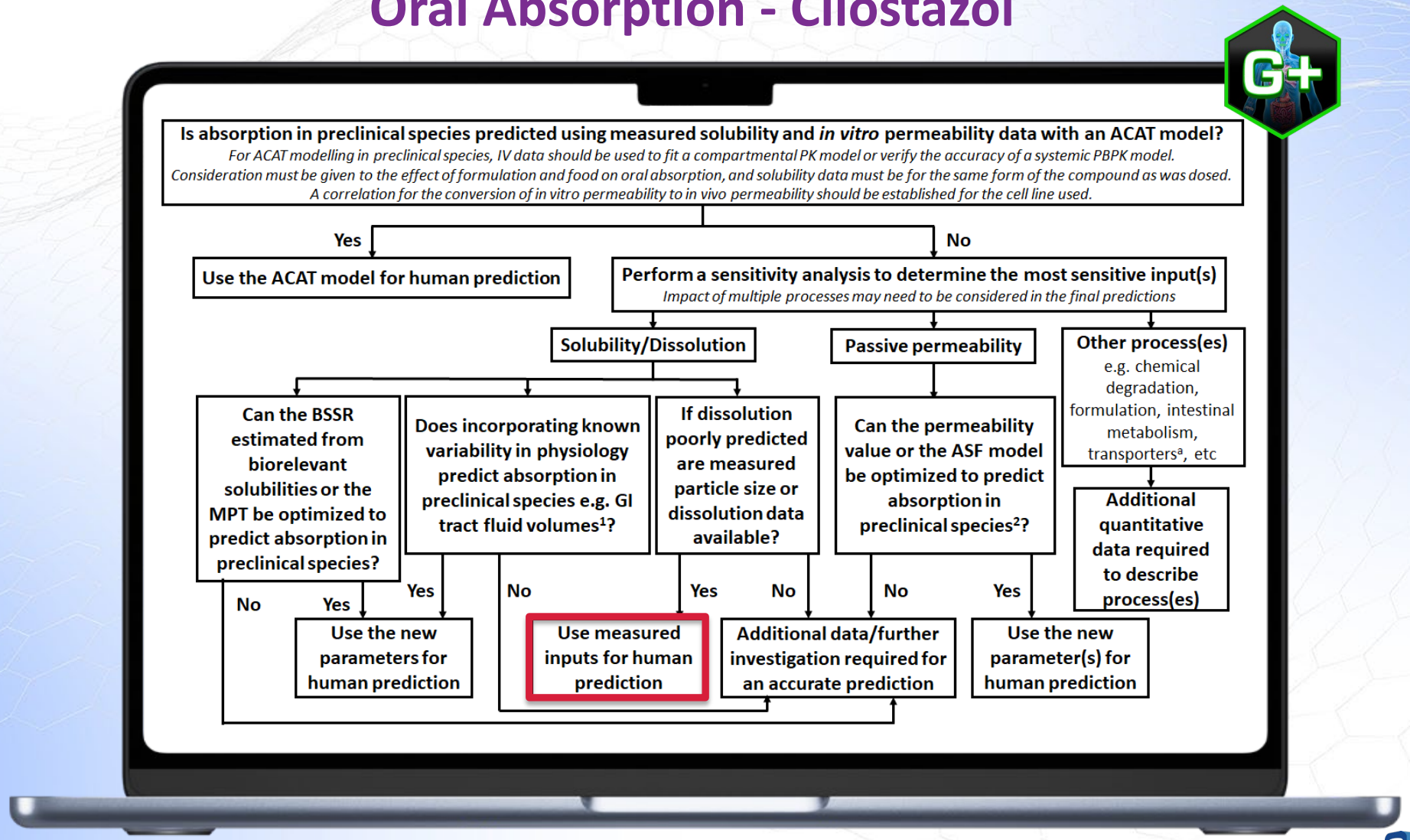


Blue – Plasma concentration
Red – Amount dissolved
Cyan – Amount absorbed

SimulationsPlus

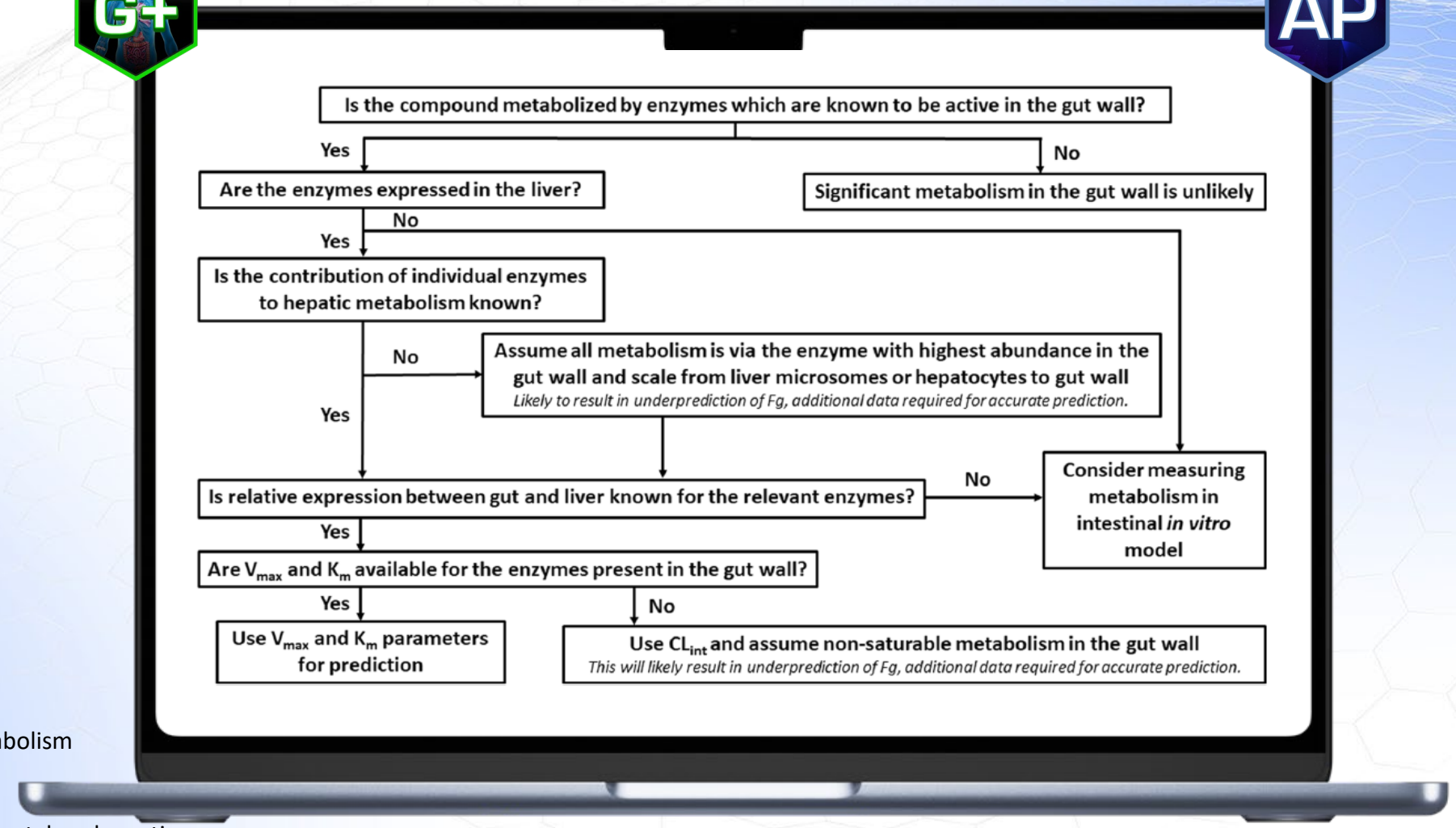
Preclinical Verification Defines Strategy for Human Prediction

Oral Absorption - Cilostazol



Preclinical Verification to Better Predict Human PK

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
- Gut wall metabolism is often saturable, and thus if V_{max} and K_m parameters are available, evaluate saturation relative to dose

Preclinical Verification: Gap Analysis

FIH prediction for PO dosing of Cilostazol : Gut Wall Metabolism

- Metabolism data
- Prediction of the human CL
- Isoforms involved in metabolism

  (from AP or in vitro data)

- CYP3A4 is predicted to metabolise Cilostazol, which is also present in the gut
- Incorporate learnings from preclinical PO modelling
- Simulate human profile using rCYP predicted clearance

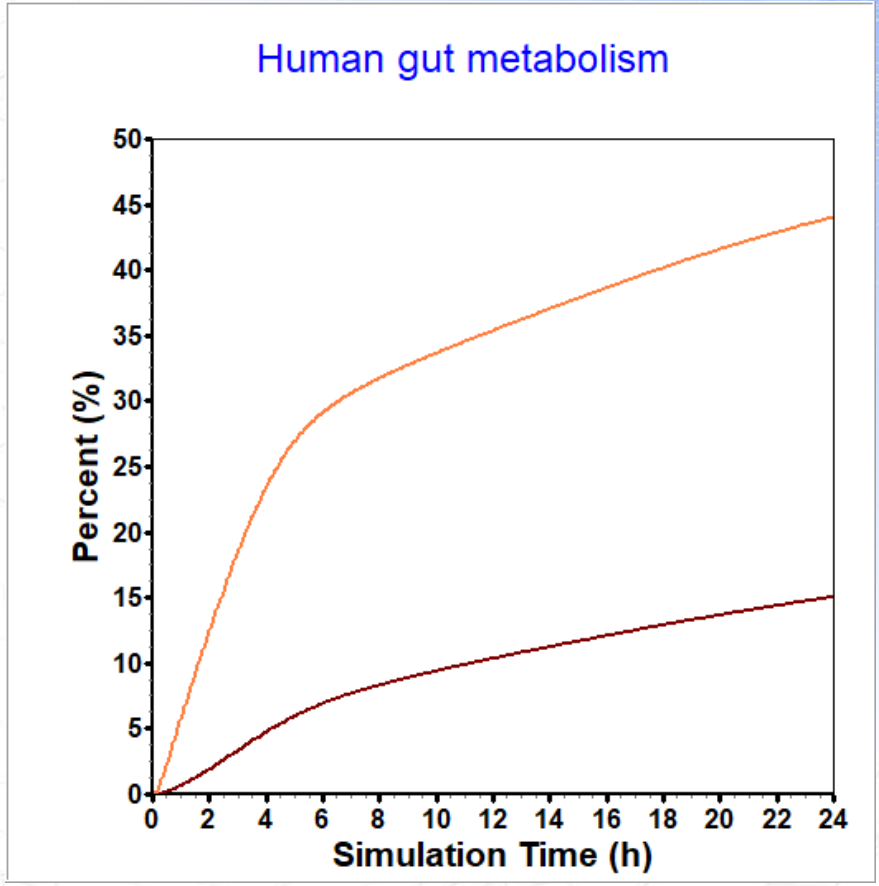
Enzyme Table

Generic	Enzyme	Location	Data Source	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)
Cilostazol	3A4	PBPK	Microsomes	0.0125	25.07
Cilostazol	3A4	Gut	Microsomes	5.53	25.07
Cilostazol	3A4	Liver	Microsomes	5.53	25.07

Preclinical Verification: Extrapolation to Human

FIH prediction for PO dosing of Cilostazol : Gut Wall Metabolism

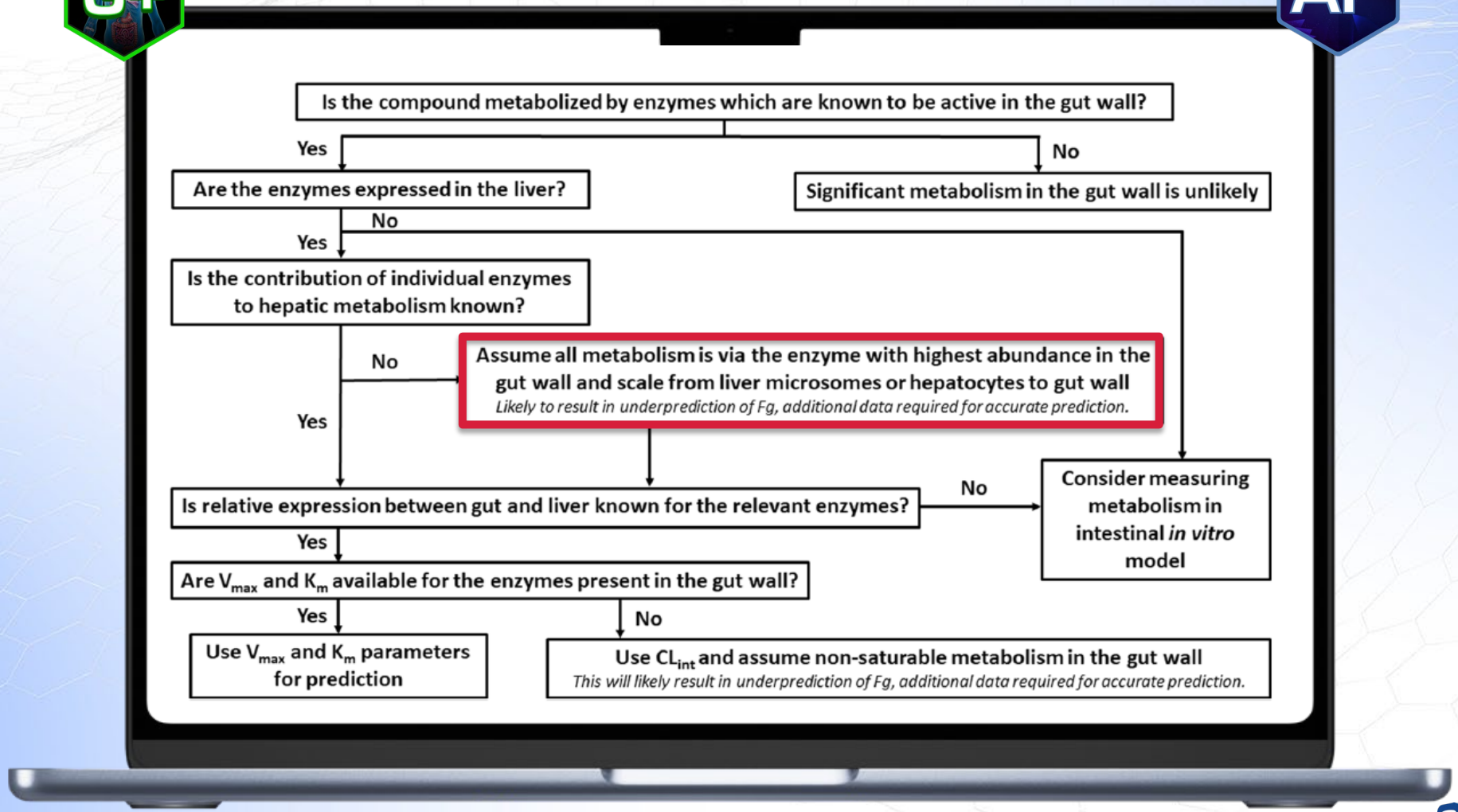
- Predicted human CLh is approximately 40% of liver blood flow
- Simulated profile using the predicted enzyme kinetics results in a Fh of ~59%
- Fg in human is predicted to be 35% indicating that gut metabolism could be a sensitive parameter



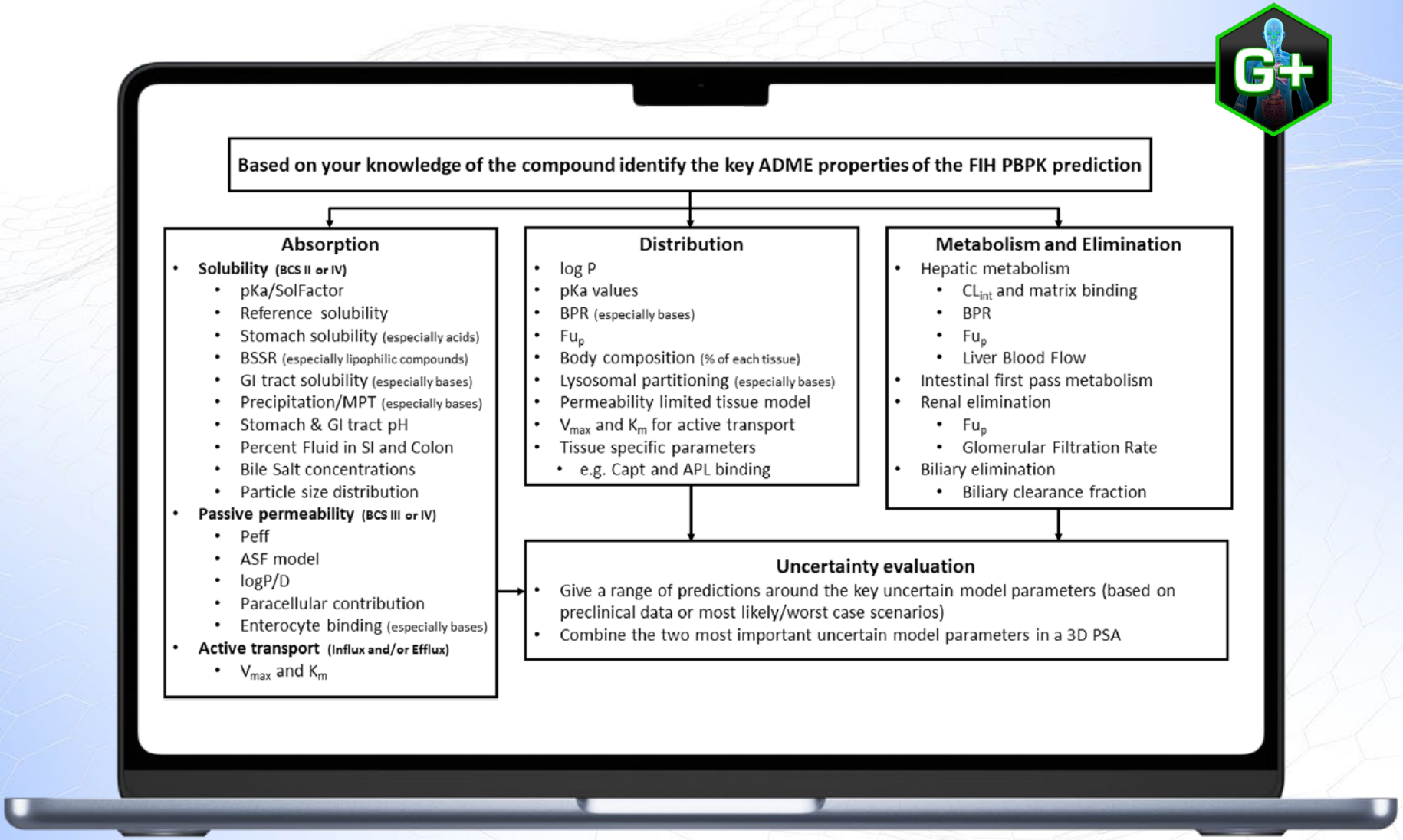
Blue – Plasma concentration
Red – Amount dissolved
Orange – % metabolised by CYP3A4 in the liver
Cyan – Amount absorbed
Purple – Amount reaching the portal vein

Preclinical Verification Defines Strategy for Human Prediction

Gut Wall Metabolism

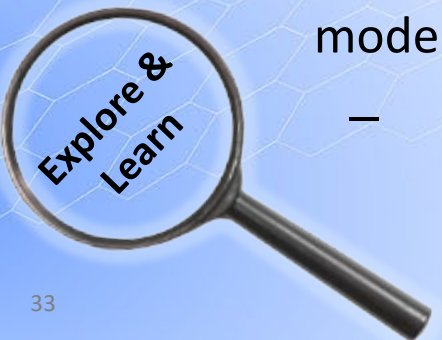


Always Include Uncertainty



Understanding the Sensitive Parameters: Planning for the Future

- Will micronisation improve the oral exposure?
- If CL or Vss is uncertain, is an IV microdose study recommended?
- Will dosing with food improve the duration of action or decrease the oral exposure?
- Will further modelling be required to understand the impact of PPI inhibitors or other medicines that increase gastric pH?
- Are there any data gaps that could be filled to give greater confidence in and utility of your model?
  - For example, reaction phenotyping of metabolising enzymes, transporter kinetics



Model Application Beyond FIH: Additional Learning

- Modelling high dose PK data in preclinical species to enable the prediction of Toxicology dose levels and frequency
  - To aid in the design of these pivotal supporting studies
- Predicting the PK in the target population in addition to healthy volunteers can inform the clinical plan
  - Populations available in the FIH Simulator include male and female, American and Asian, infant and paediatric, healthy, obese, hepatically and renally impaired

Model Application Beyond FIH: Inform Your Clinical Plan

- Models developed using the FIH Simulator can be used to:
  - predict the possibility of DDIs with your test compound as the victim or the perpetrator
  - Consider additional dosage routes
- This does require the purchase of additional modules

Regulatory Applications

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Organizations
(innovator & generic companies combined)

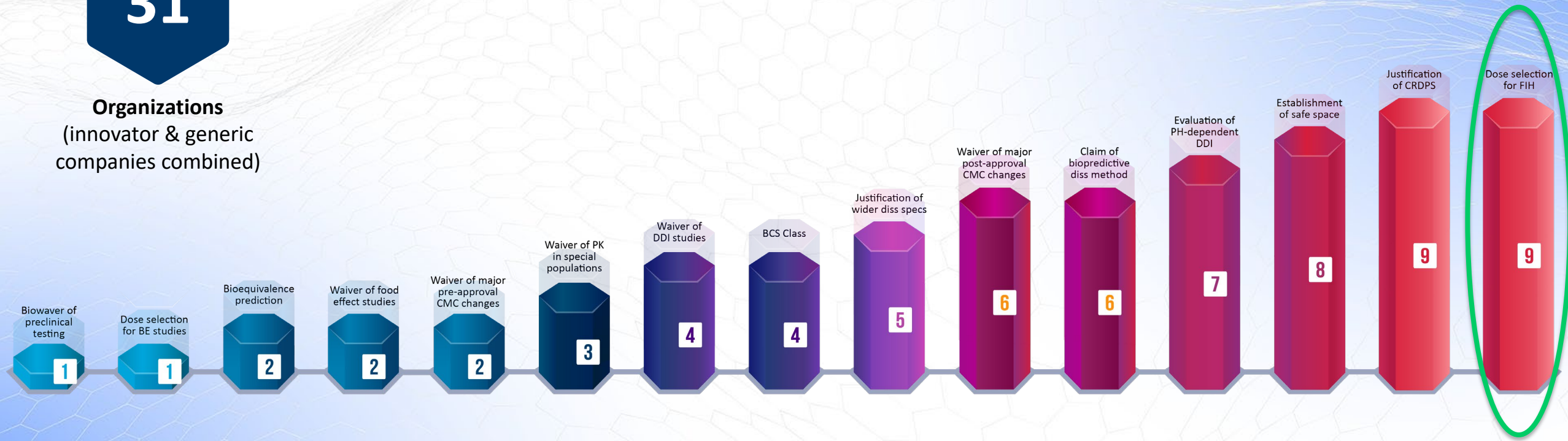

Fig. 1 Regulatory Applications of GastroPlus® (PBBM/PBPK Modeling) in the Pharmaceutical Industry (Years 2020-2022): Results from Survey

Considerations

- **Use everything that you know, but keep the model as simple as possible**
  - Aim to use PBPK not empirical modelling
  - Combine compound specific data with physiology as they are intimately interconnected and explicable only by reference to the whole
- **Preclinical verification can increase the accuracy of the human prediction but will always lead to learning**
- **Always include uncertainty**
  - Never give single point estimates
- **Be realistic with your expectations**
  - A successful prediction gets the category right or within 2-fold, but not necessarily matching values exactly
- **Sensitivity analysis and model application can inform future decisions**
  - Apply model to gain insight into potential development questions

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Thank You

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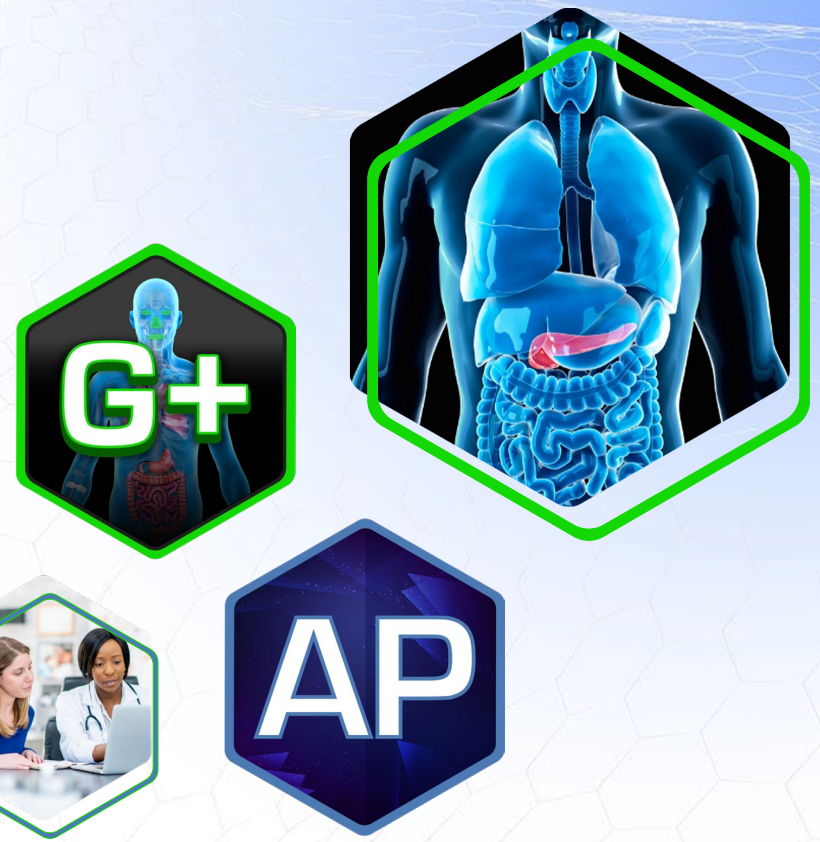

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