Basics of PBPK Modelling and Introduction to GastroPlus® X & its integration with AI

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Principal Scientist and Scientific Lead – India

Physiologically Based Pharmacokinetic (PBPK) Solutions

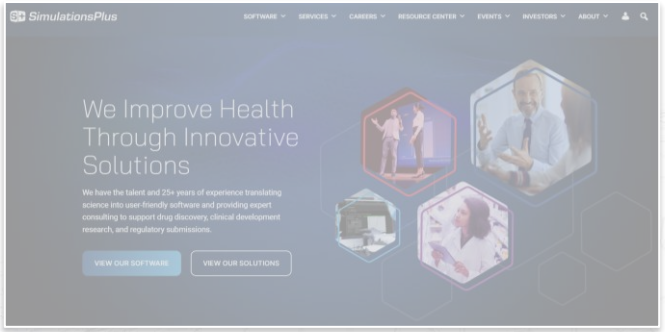
One-Day National Seminar on "AI in Pharmaceutical Development“

@NGSM Institute of Pharmaceutical Sciences, Mangalore

12-September-2025

Agenda

- Simulations Plus:
  - Who are we?
  - Where can we help?
- Definitions and Context
- Overview of Mechanistic Processes in GastroPlus®
- GastroPlus®X Next-Level PBPK
  - GPX Paradigm and Terminologies
- Integration of GPX with AI



Worldwide Model-Informed Drug Development

Our reputation as thought leaders in the areas of ADMET property prediction, physiologically-based pharmacokinetics (PBPK) modeling, pharmacometrics, and quantitative systems pharmacology/toxicology is earned through the success our clients have found through their relationship with us. We have the talent and 25+ years of experience translating science into user-friendly software and providing expert consulting to support drug discovery, clinical development research, and regulatory submissions.

Simulations Plus Inc.

Innovative science-based software

VIEW ALL SOFTWARE

GastroPlus® PBBM/PBPK | ADMET Predictor® AIDD/ML | DILIsym® QST | MonolixSuite™ PK/PD | NAFLDsym® QSP

GastroPlus is a mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal, subcutaneous, and intramuscular absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals.

- Drug Drug Interaction™
- PBPKPlus™
- ADMET Predictor®
- Additional Dosage Routes
- Metabolism & Transporter
- Biologics
- Optimization
- PDPlus™
- PKPlus™
- IVIVCPlus™

Consulting Services

QSP/QST Consulting Services

Custom software for predicting efficacy and guiding design (QSP).

PK/PD Consulting Services

Providing an expert review and second set of eyes to quality check your modeling efforts.

Who We Are

NASDAQ: SLP

- **Cheminformatics (CHEM)**
  Software & Services
- **Physiologically Based Pharmacokinetics (PBPK)**
  Software & Services
- **Clinical Pharmacology & Pharmacometrics (CPP)**
  Software & Services
- **Quantitative Systems Pharmacology (QSP)**
  Software & Services
- **Adaptive Learning & Insights (ALI)**
  Software & Services
- **Medical Communications (MC)**
  Software & Services

>280 Pharmaceutical, biotechnology, chemicals, cosmetics, & consumer goods companies in the U.S., Europe, Asia, and South America

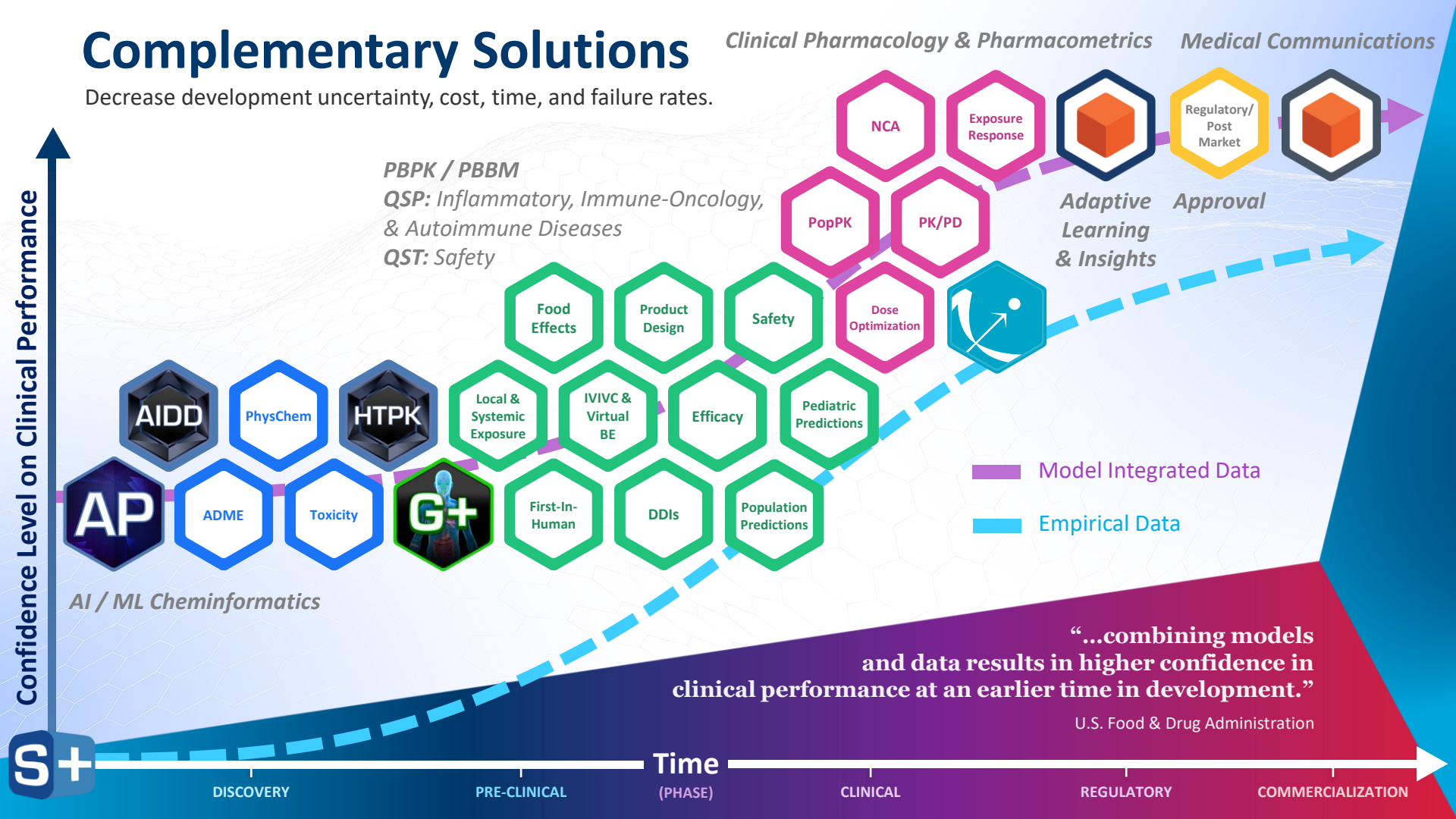
200+ Employees Worldwide

>25 yrs. Established In 1996

SimulationsPlus

Complementary Solutions

Decrease development uncertainty, cost, time, and failure rates.



"...combining models and data results in higher confidence in clinical performance at an earlier time in development."

U.S. Food & Drug Administration

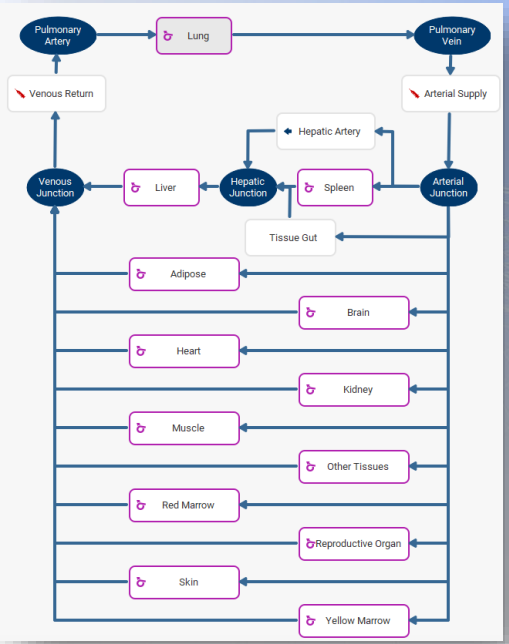
Definitions and Context

PBPK M&S and PBBM

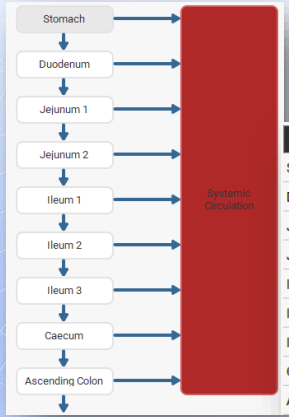
- PBPK Modelling: **P**hysiologically **B**ased **P**harmaco**K**inetic Modelling
  - A mathematical modelling technique for predicting the ADME of synthetic or natural chemical substances in humans and other animal species
  - The baseline model that combines physiology, population, and drug characteristics to mechanistically describe the PK and/or pharmacodynamic behaviors
- PBBM: **P**hysiologically **B**ased **B**iopharmaceutics **M**odelling
  - Establishing the link between bio-predictive *in-vitro* dissolution testing and mechanistic oral absorption modelling
    - Mechanistic implementation of formulation/manufacturing aspects that are relevant to dissolution/release from the drug product
    - Verifying whether the dissolution method of the pharmaceutical product is bio-predictive or clinically relevant
  - The application of the baseline (PBPK) model to support drug product development – e.g., IVIVCs, virtual bioequivalence

PBPK & PBBM

- Describes the body as a system of compartments with respect to absorption and drug disposition
  - Requires:
    - Drug-specific parameters
    - Formulation-specific parameters
    - System-specific/physiological parameters



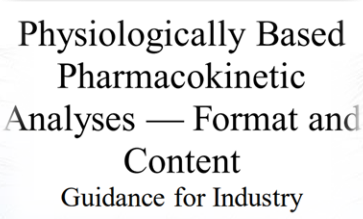
GastroPlus® PBPK Model Structure



GastroPlus® ACAT Model Structure

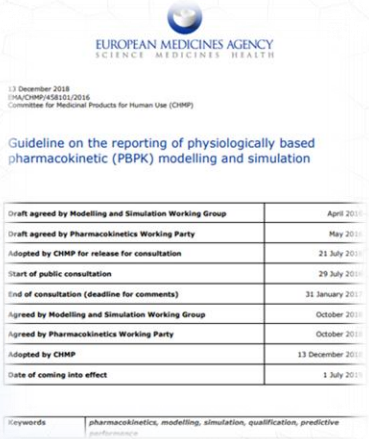
Compartment	Permeability (cm/s)	ASF (1/cm)	$f_{u,ent}$	pH	Transit Time (h)	Volume (mL)	Length (m)	Radius (m)	SEF	Bile Salt (mmol/L)	Pore Radius (Å)	Pore Length (cm)	Porosity	Electric Potential Gradient	Compartment Type
Stomach		0	1	1.3	0.25	49.44	0.2943	0.09923	1	0	2.2	0.3876	1	0.102	Stomach
Duodenum		2.685	1	6	0.2586	45.41	0.1469	0.01568	4.235	2.8	10.41	0.02056	1	0.102	Intestinal
Jejunum 1		2.647	1	6.2	0.9374	170.1	0.6075	0.01493	3.949	2.33	9.64	0.02571	1	0.102	Intestinal
Jejunum 2		2.657	1	6.4	0.7435	133.4	0.6075	0.01322	3.489	2.03	8.4	0.03833	1	0.102	Intestinal
Ileum 1		2.627	1	6.6	0.5818	104.1	0.6075	0.01168	3.029	1.41	7.16	0.06075	1	0.102	Intestinal
Ileum 2		2.621	1	6.9	0.4202	76.68	0.6075	0.01002	2.569	1.16	5.92	0.1048	1	0.102	Intestinal
Ileum 3		2.586	1	7.4	0.2909	54.62	0.6075	8.458e-03	2.109	0.14	4.68	0.2042	1	0.102	Intestinal
Caecum		0.7177	1	6.4	4.4	51.29	0.1357	0.03468	1.79	0	3.92	0.3431	1	0.102	Colon
Ascending Colon		2.09	1	6.8	13.2	54.41	0.2852	0.02464	2.48	0	3.5	0.3106	1	0.102	Colon

Mechanistic Modelling to Support Regulatory Interaction: The Push!


Physiologically Based Pharmacokinetic Analyses — Format and Content
Guidance for Industry

https://www.fda.gov/media/101469/download

2018


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

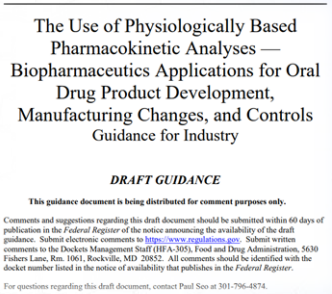
13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

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

Draft agreed by Modelling and Simulation Working Group	April 201
Draft agreed by Pharmacokinetics Working Party	May 201
Adopted by CHMP for release for consultation	21 July 201
Start of public consultation	29 July 201
End of consultation (deadline for comments)	31 January 201
Agreed by Modelling and Simulation Working Group	October 201
Agreed by Pharmacokinetics Working Party	October 201
Adopted by CHMP	13 December 201
Date of coming into effect	1 July 201
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

2018


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

DRAFT GUIDANCE

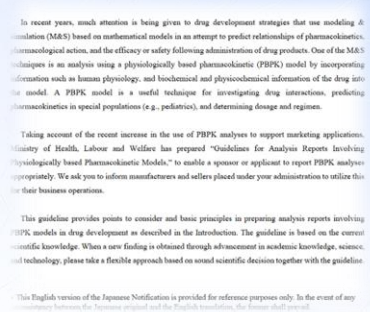
This guidance document is being distributed for comment purposes only.

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.

https://www.fda.gov/media/142500/download

2020


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 in 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 discrepancy between the Japanese original and the English translation, the former shall prevail.

https://www.pmda.go.jp/files/000239317.pdf

2020

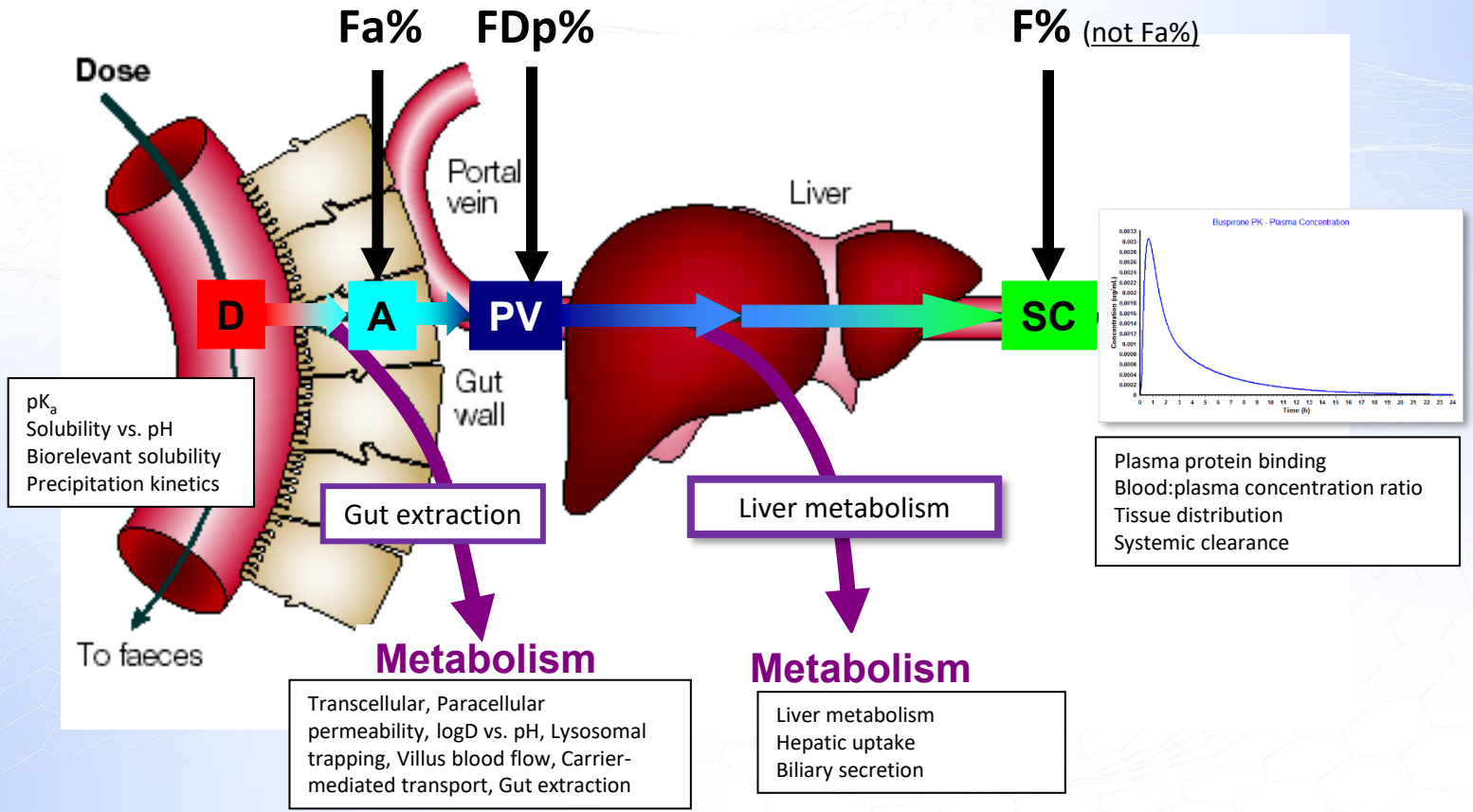
DiBella J. 22nd IDMA-APA Pharmaceutical Analysts Convention (PAC) (2023)

SimulationsPlus

GastroPlus® and an Overview of Mechanistic Processes

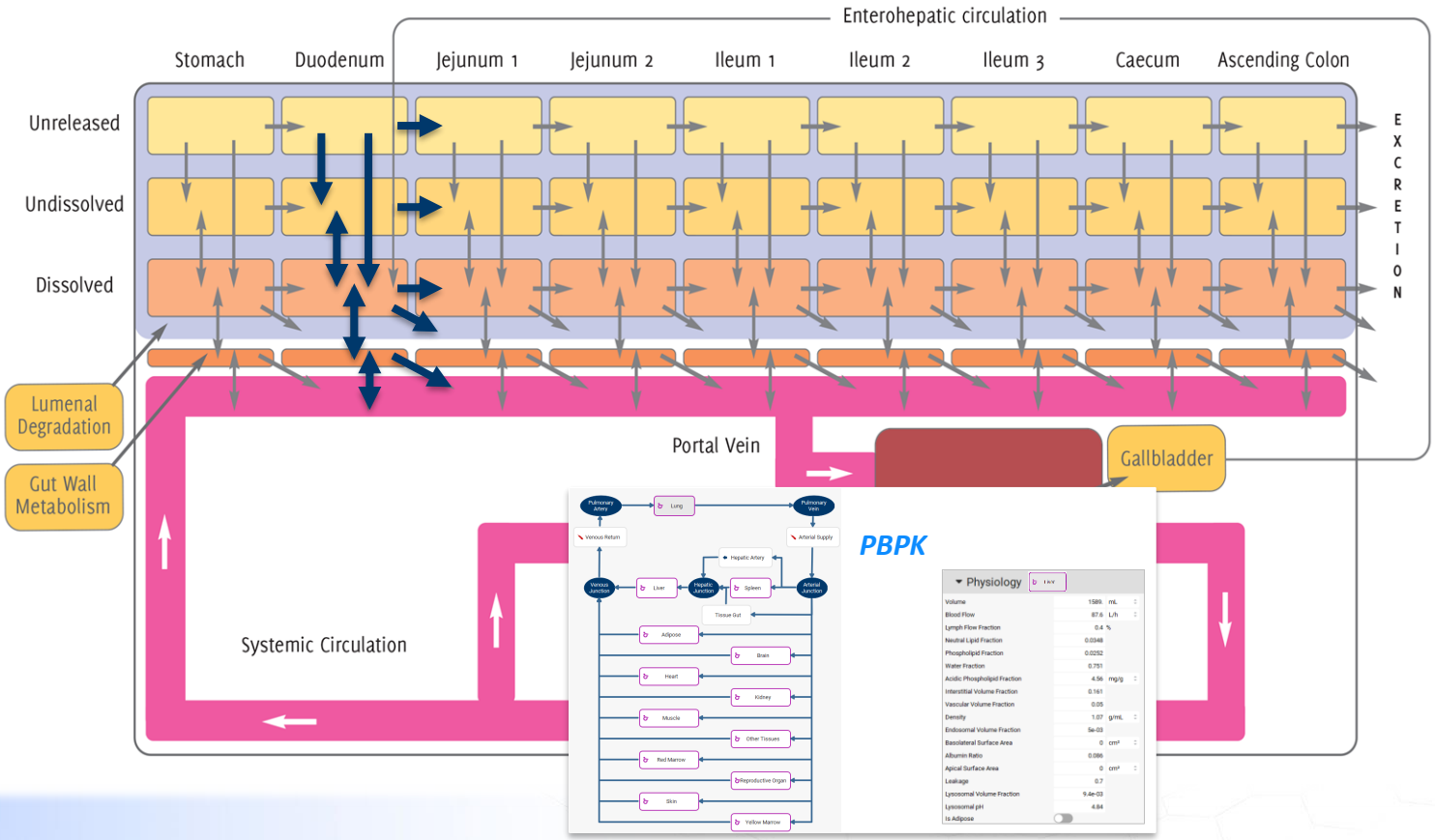
Oral Absorption Modelling

What is happening *in-vivo*?



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

Advanced Compartmental Absorption and Transit Model (ACAT™)



SimulationsPlus

The Big Picture

Structure → *in silico*

in vitro experiments

Formulation: Dose, dosage form, particle size, release profile

in vitro metabolism

Structure → *in silico*

Physical properties: Peff, Sw, pKa, logP, fup, Rbp

PKPlus™: Vd, CL, K12, K21, K13, K31
PBPKPlus™ : CLint

IV/Oral PK data

in vitro constants:
Vmax(s), Km(s), Ki(s), EC50, etc…

Scale to *in vivo* processes

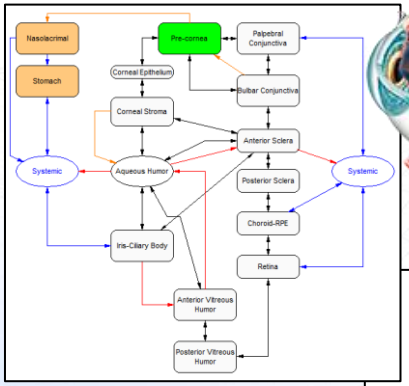
Therapeutic/Adverse Effect Data

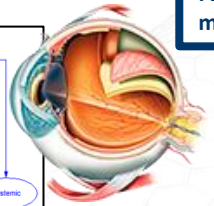
Dissolution and absorption
Plasma/tissue concentration profiles
Nonlinear kinetics and DDI
PBPK/PD modeling

SimulationsPlus

Pathways Beyond Oral Absorption…

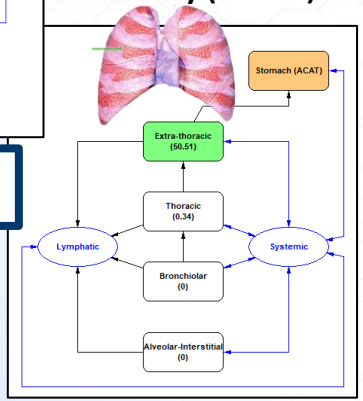
Ocular (OCAT™)





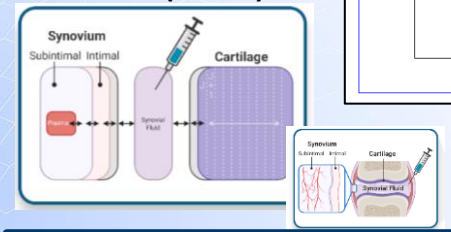
FDA: Ocular model extensions

Pulmonary (PCAT™)

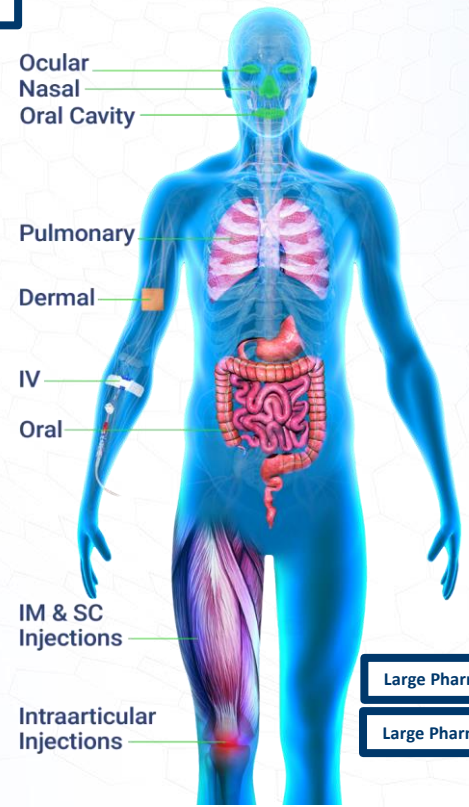


FDA: Pulmonary model extensions

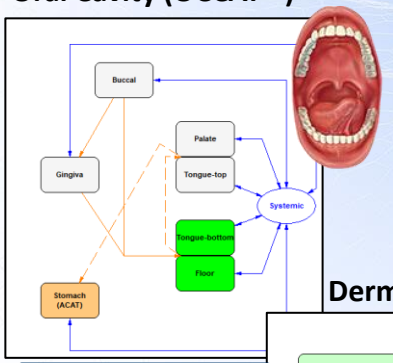
Intraarticular (ICAT™)



FDA: Long-acting injection model extensions



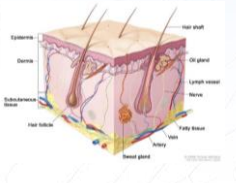
Oral Cavity (OCCAT™)

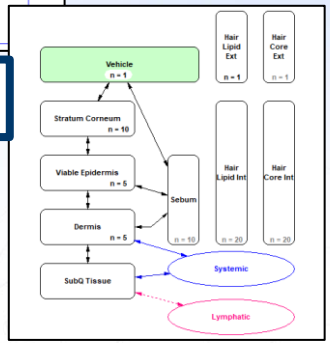


FDA: Oral cavity model extensions

FDA: Dermal model extensions

Dermal (TCAT™)





Large Pharma: ACAT™ model extensions

Large Pharma: Local GI disease extensions

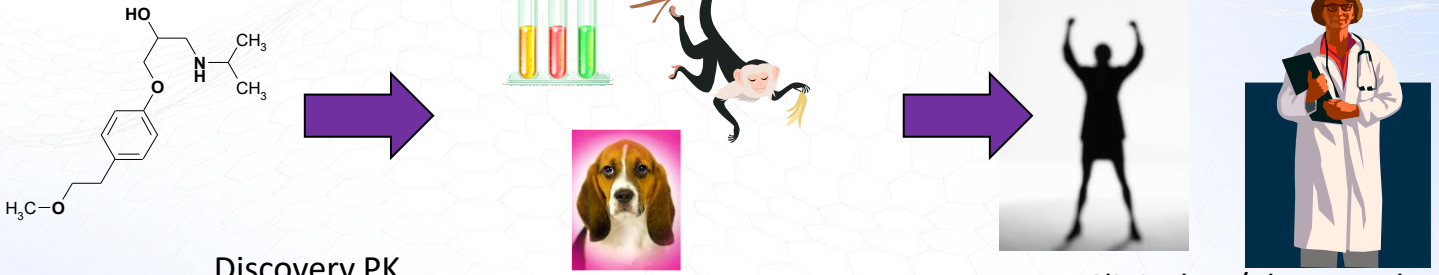
FDA: Oral absorption model extensions

Large Pharma: Virtual BE trial simulator

SimulationsPlus

Where is GastroPlus® Being Used Today?

Discovery **Preclinical** **Clinical**



Discovery PK

- Combine *in silico* technologies to screen compound libraries in animals or humans
- Incorporate preclinical/*in vitro* data for First In Human (FIH) predictions/IVIVE
- Identify toxic dose levels in preclinical species

Clinical PK/Pharmacology

- Simulate population behaviors (e.g., pediatrics, disease)
- Build PBPK-PD models
- Predict Drug-Drug Interactions (DDIs)

Pharmaceutical Development

- Assess various strategies during formulation development
- Assist with Quality by Design (QbD) implementation
- Develop mechanistic *in vitro-in vivo* correlations (IVIVCs)
- Understand food effects
- Establish drug product specifications and safe spaces

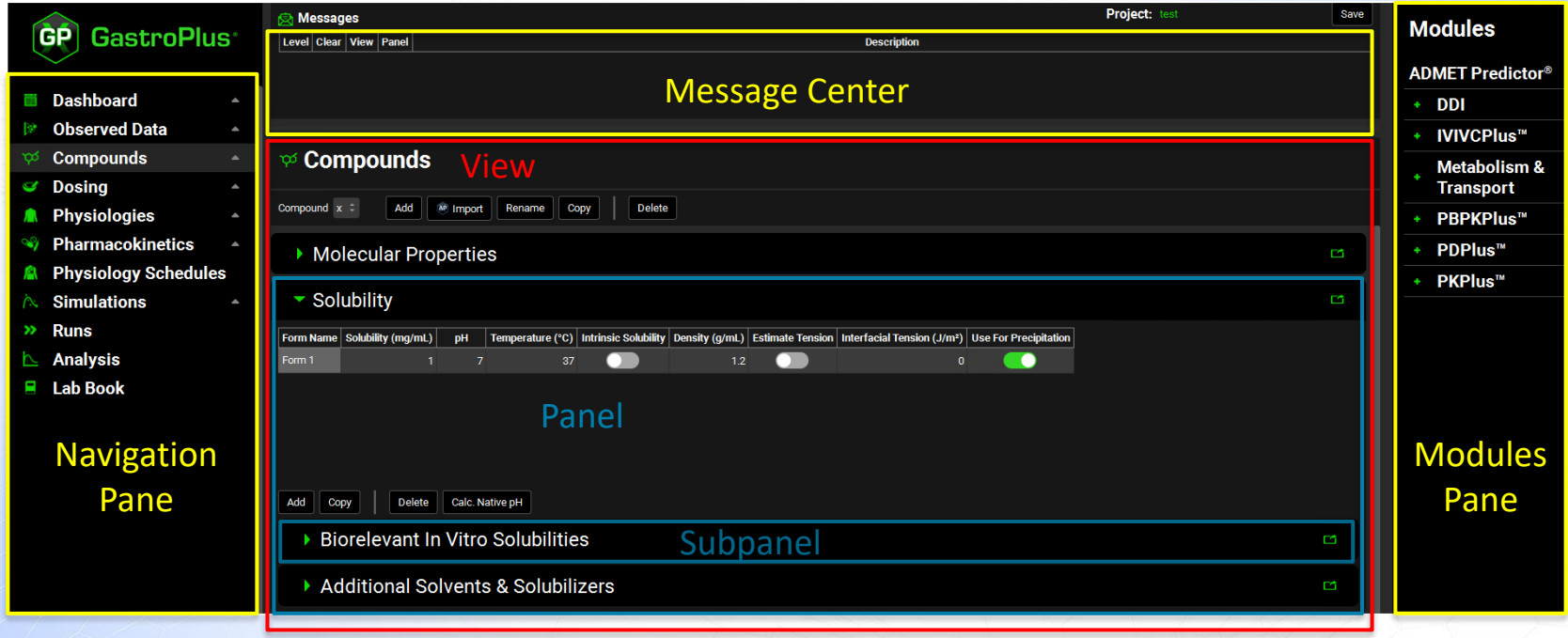
GastroPlus®X Next-Level PBPK

GPX Paradigm and Terminologies

Two main concepts:

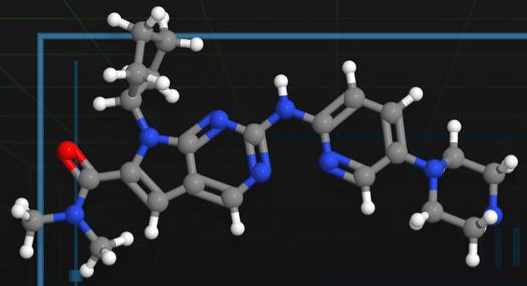
- One screen with 2 side panes (Navigation and Modules) and vertical scrolling
- Reusable assets

GPX Terminology



SimulationsPlus

What goes into a simulation?



Compound

Formulation

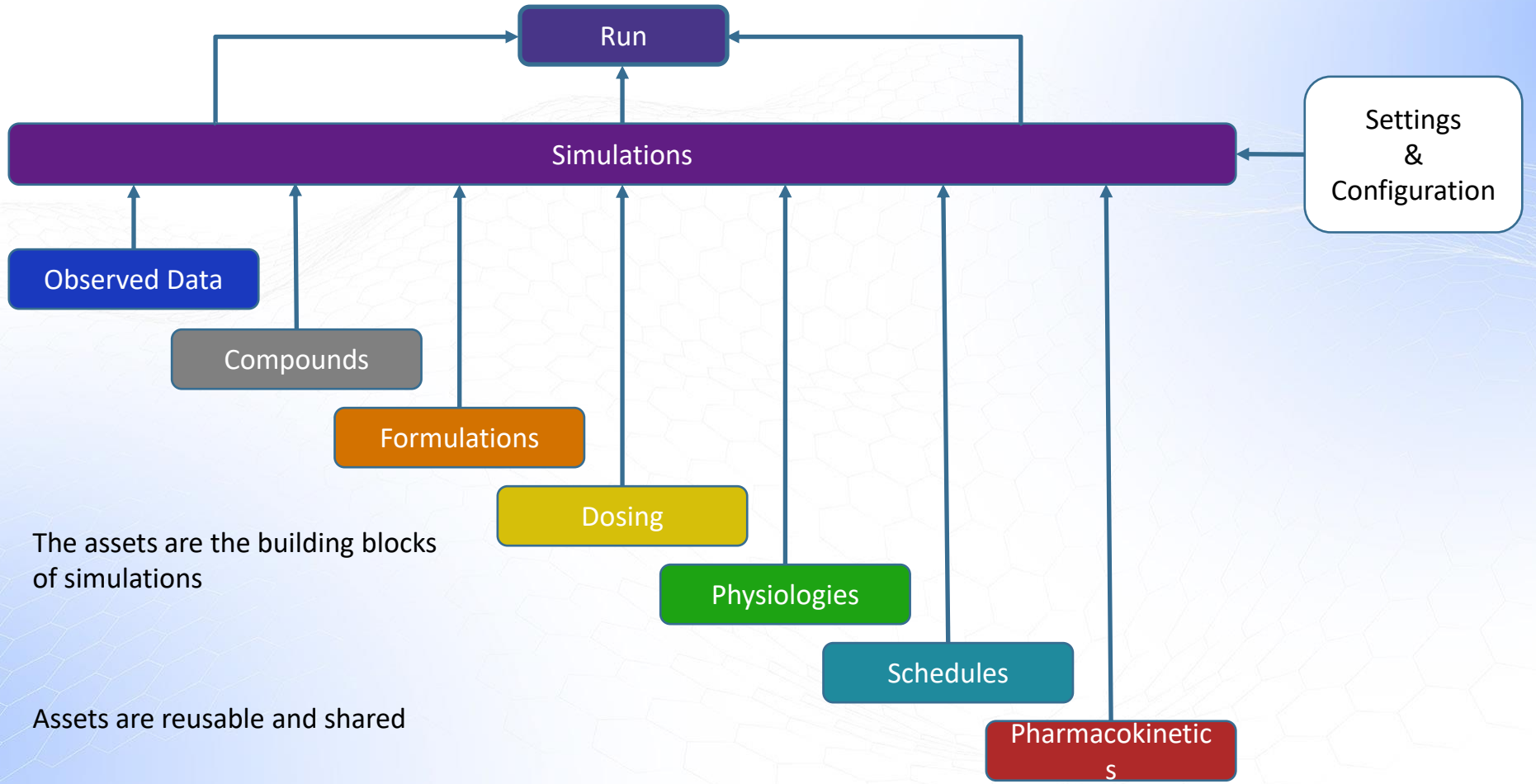
Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

Dose

Schedule

Physiology



The assets are the building blocks of simulations

Assets are reusable and shared

Reusable Assets

Compound X in silico

Compound X in vitro

Compound X enz

IV bolus

Tablet

IV bolus 10 mg

Tablet 100 mg

Tablet 50 mg

Cpt 1

Cpt 2

PBPK perf

Fast HumMal75kg

Fed HumMal75kg

Fast HumFem62kg

Phys sched Fast Mal

Phys sched Fast Fem

Phys sched Fed Mal

Obs IV 10mg Mal

Obs Tab 100mg Fem

Obs Tab 50mg Mal Fast

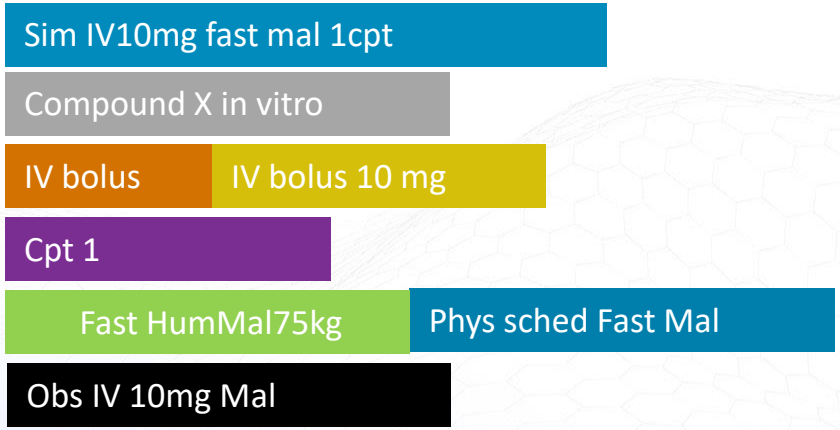
Obs Tab 50mg Mal Fed

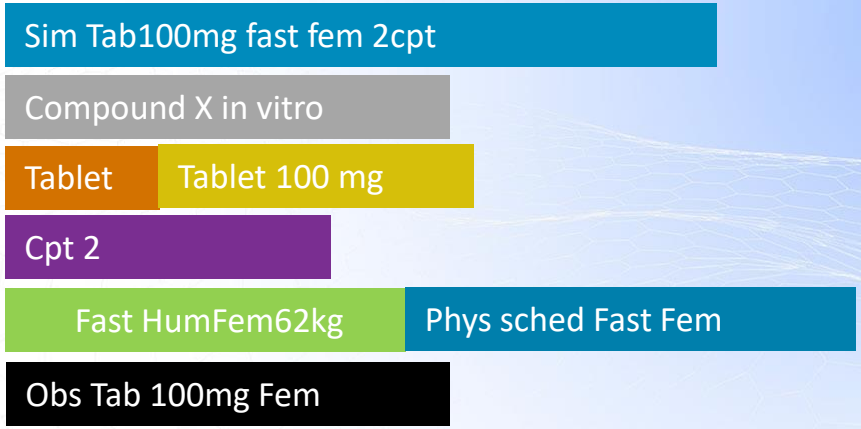
Sim IV10mg fast mal 1cpt

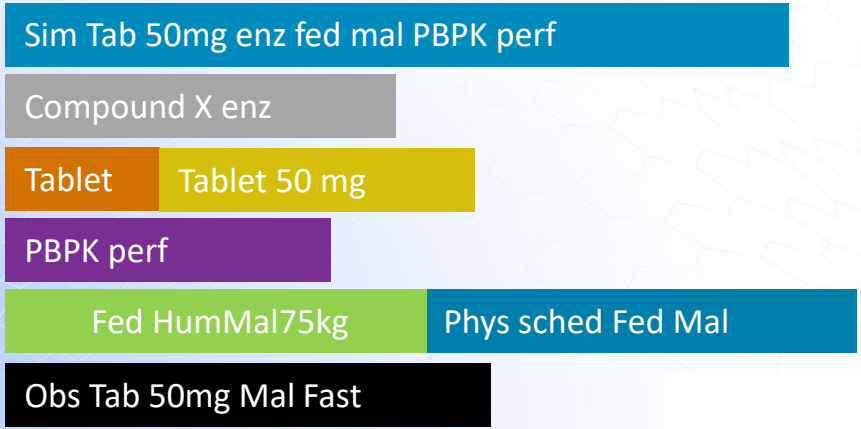
Sim Tab100mg fast fem 2cpt

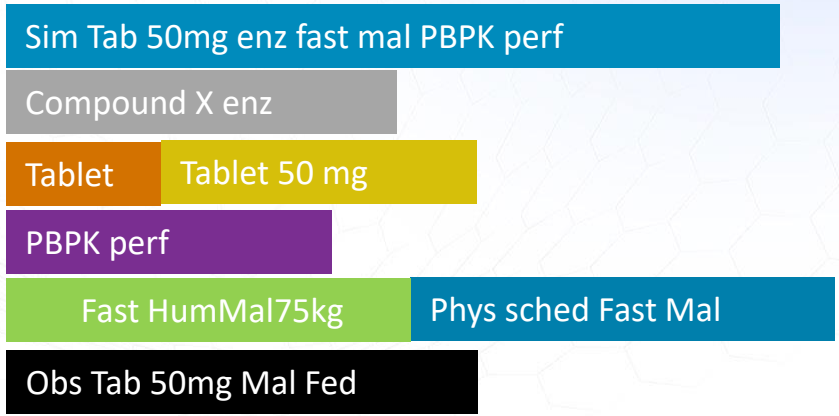
Sim Tab 50mg enz fast mal PBPK perf

Sim Tab 50mg enz fed mal PBPK perf


Sim IV10mg fast mal 1cpt
Compound X in vitro
IV bolus
IV bolus 10 mg
Cpt 1
Fast HumMal75kg
Phys sched Fast Mal
Obs IV 10mg Mal

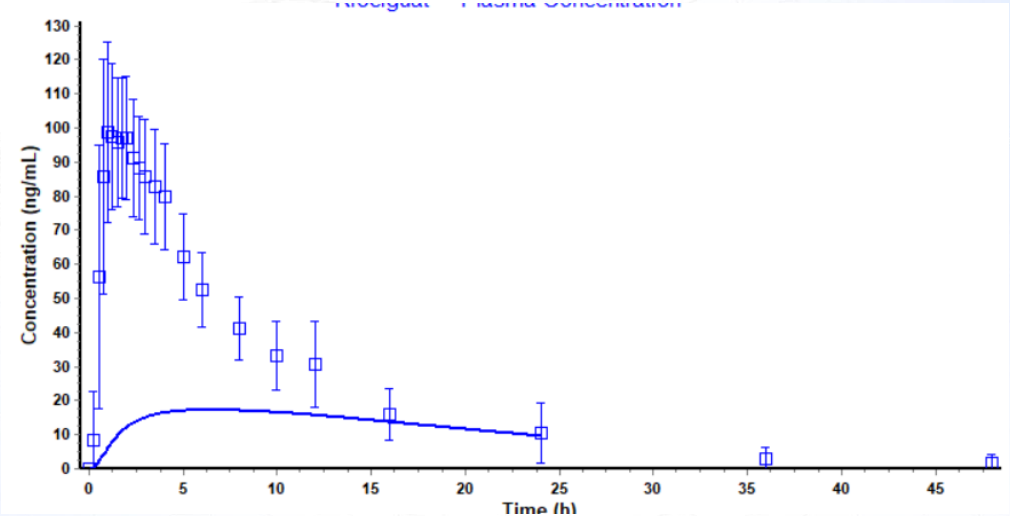

Sim Tab100mg fast fem 2cpt
Compound X in vitro
Tablet
Tablet 100 mg
Cpt 2
Fast HumFem62kg
Phys sched Fast Fem
Obs Tab 100mg Fem


Sim Tab 50mg enz fed mal PBPK perf
Compound X enz
Tablet
Tablet 50 mg
PBPK perf
Fed HumMal75kg
Phys sched Fed Mal
Obs Tab 50mg Mal Fast


Sim Tab 50mg enz fast mal PBPK perf
Compound X enz
Tablet
Tablet 50 mg
PBPK perf
Fast HumMal75kg
Phys sched Fast Mal
Obs Tab 50mg Mal Fed

The Intersection of AI and PBPK Modeling @ Simulations Plus

“I would like to kindly request a meeting to receive some guidance regarding a new project that we are currently working on, where we are getting very poor predictions, please see below.”



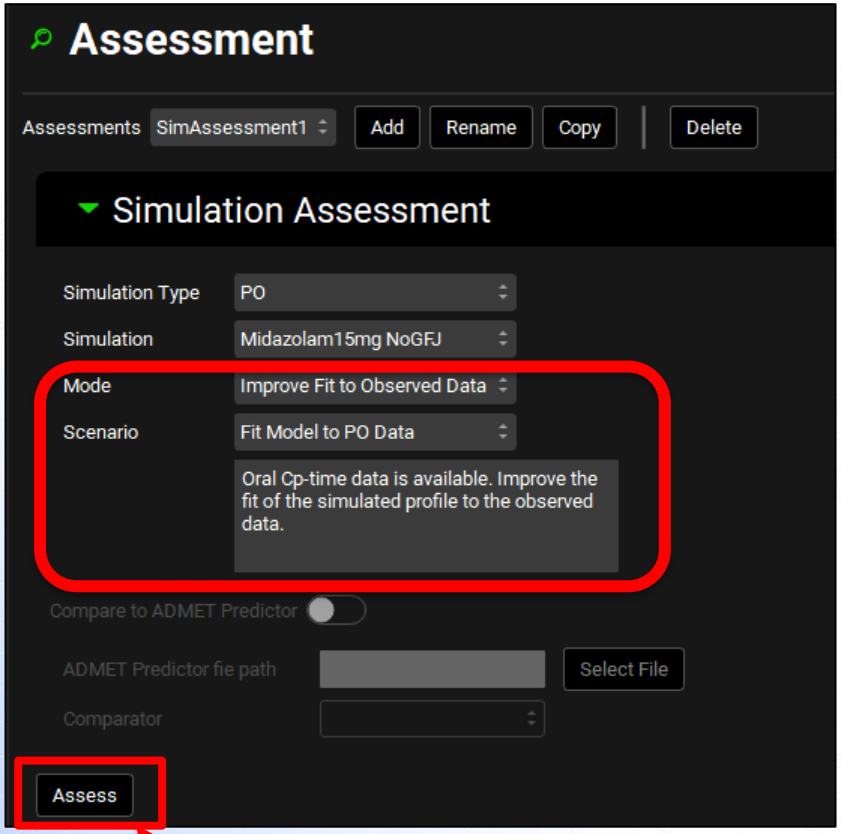
What happens today…

- Initial support meeting scheduled to assess
- T&M contract executed to provide coaching and model-building guidance
- Recurring meetings scheduled over weeks to manually iterate to land on final model
- Reports are manually constructed with tables/figures/lists exported from GastroPlus

What happens tomorrow…

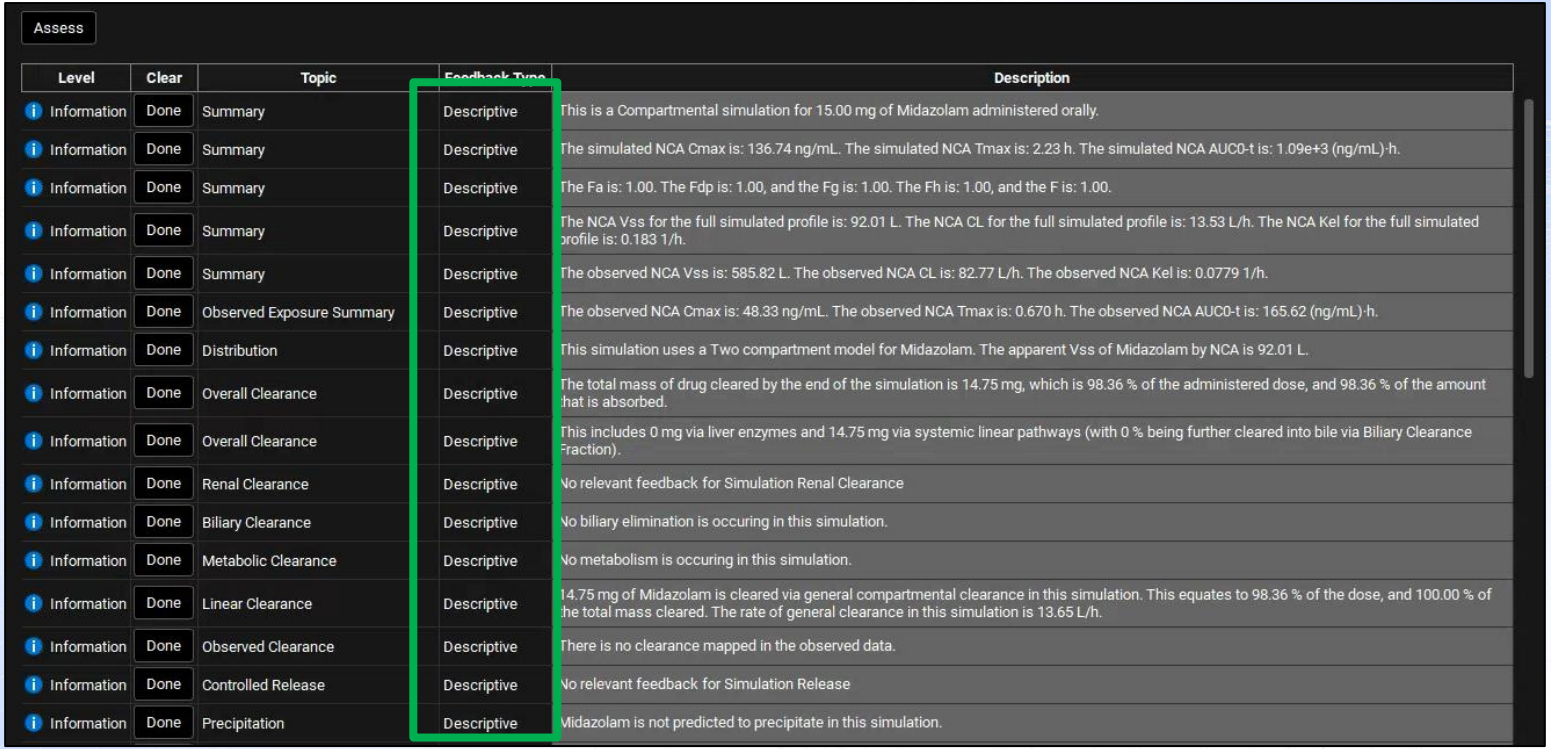
- Data extracted from reports/publications and, with chemical structure + in vitro data, loaded into GastroPlus AssessmentsPlus™ Module
- AI-inspired assessment offers guidance on parameters and mechanisms driving mis-prediction
- Prompts into integrated GastroPlus AI Agents Module automate the initial model selection and optimize to the final parameter set
- AI-powered Report Engine Module produces internal (or submission-ready) reports
- T&M contract to support model guidance and customized automation as needed – e.g., tuned AI agents

AI in PBPK Solutions



Click to run the assessment

Set up a simulation assessment, to get advice for improving the fit of the PO simulation to the observed Cp-time profile



Description of “what happened” in the simulation

Level	Clear	Topic	Feedback Type	Description
Caution	Done	Warning	Setup	The observed data does not include CVs. The advice obtained may be more appropriate if a mean profile with CVs is used.
Information	Done	Summary	Actionable	AUC is underpredicted, and may be explained by an error in fraction absorbed.
Information	Done	Simulated vs. Observed Summary	Actionable	The predicted AUC0-t is 1.45e+3 (ng/mL)·h, and the observed AUC0-t is 2.20e+3 (ng/mL)·h. The predicted / observed AUC0-t ratio is 0.659. The AUC is thus underpredicted for the dose of 150.00 mg. There are multiple reasons that could lead to this situation.
Information	Done	Permeation	Actionable	The fraction absorbed may be limited by passive permeability. Please check how the drug permeability was parameterized in the model. You may use PK profiles obtained with an oral solution where precipitation is not expected to happen to check your permeability data using a top-down approach.

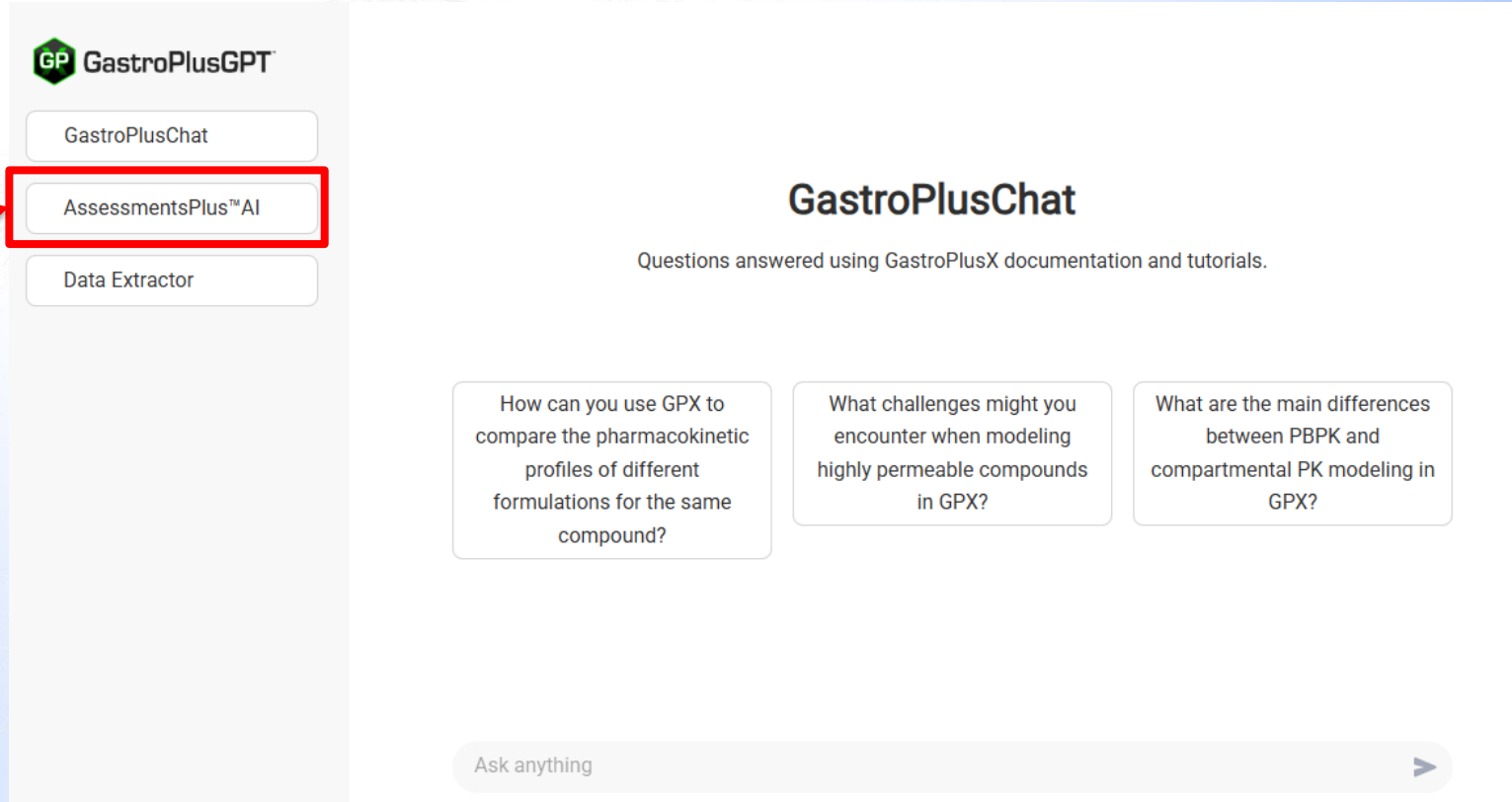
Actionable feedback for the user to enact

Copy for AssessmentsPlus AI

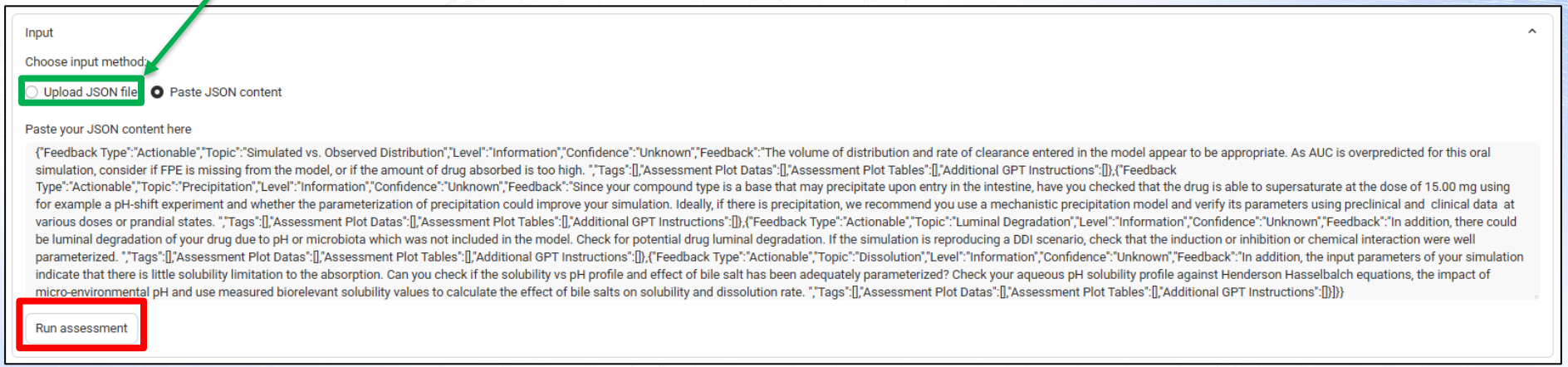
Launch AssessmentsPlus AI

Most Important Part: Get it ready to send to AI

Select the AssessmentsPlus AI application



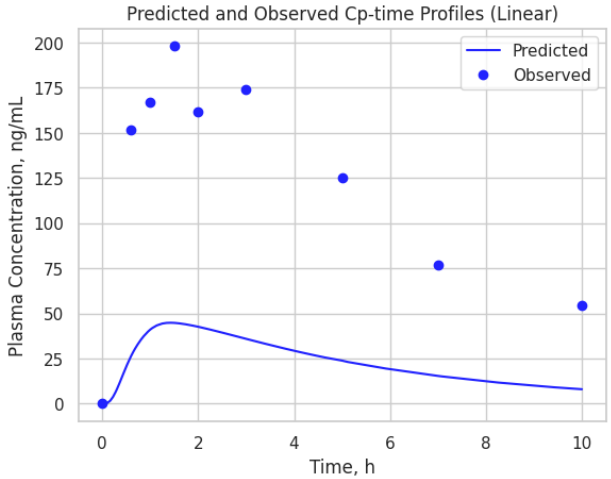
Can also upload saved results



Click to run the AI enhancement

AI Summary

- **Overview**: The simulation, conducted as a compartmental model for 156.16 mg oral Metoprolol Tartrate, reveals significant discrepancies between predicted and observed plasma concentration-time profiles. Key ratios show that Cmax and AUC0-t are underpredicted, with a predicted/observed AUC ratio of 0.203. There is also a notable overprediction in simulated NCA Vss (approx. 3000 L) and NCA CL (approx. 570 L/h) compared to observed values (701.47 L and 105.65 L/h respectively). The observed data present high variability (CVs >90%) and a secondary peak in the concentration profile that could be due either to enterohepatic circulation or data variability. The model suggests low fraction absorbed (15.65%) primarily due to luminal degradation and active efflux via P-gp.



AI Summary gives an overview of the simulation, followed by a discussion of absorption, distribution, and clearance processes and pathways. Plots and tables provide the data for in-line context.

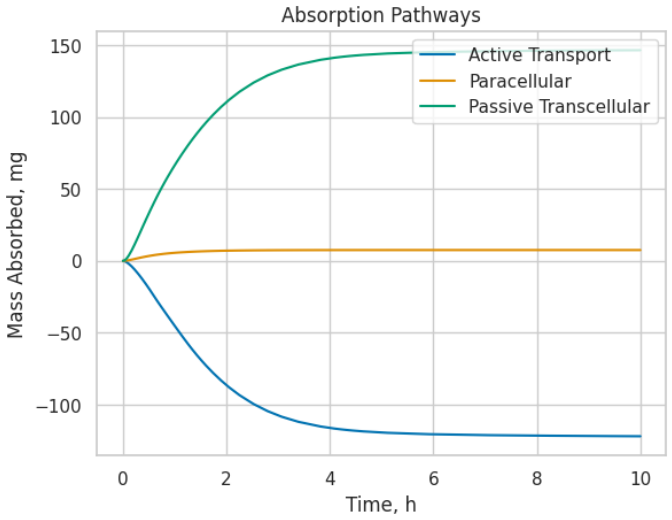
- **Executive Summary**: The simulation of oral Metoprolol Tartrate using a compartmental model exhibits clear discrepancies with the observed data, notably in exposure (AUC) and predicted pharmacokinetic parameters. There is a significant underprediction of AUC and peak concentrations, along with overpredicted NCA Vss and clearance. The analysis indicates that extensive luminal degradation and active efflux via P-gp are key factors limiting drug absorption. Observed high data variability and a secondary peak introduce additional uncertainty in model performance. Adjustments in both absorption and distribution parameters are imperative. In particular, re-evaluation of luminal degradation conditions and transporter kinetics is advised. The compartmental model's inherent coupling of clearance and volume estimates calls for a simultaneous re-assessment of these parameters. Recommendations are provided to refine model predictions. This simulation highlights the importance of mechanistic input accuracy in improving prediction quality.

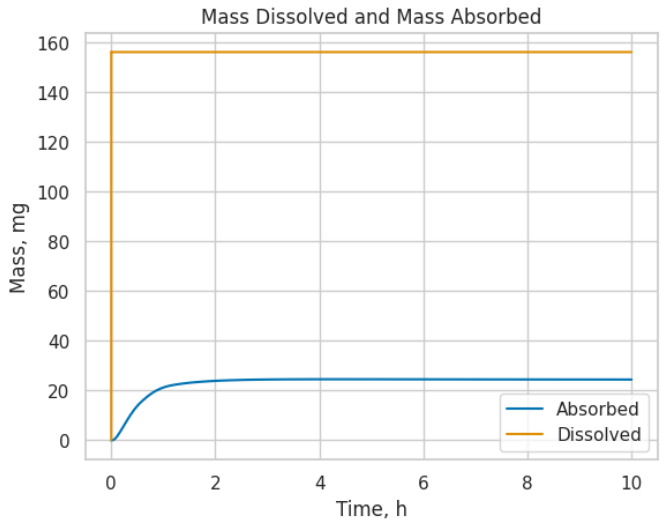
Export AI Summary to Markdown

Export AI Summary to PDF

Can generate a downloadable report

- **Permeation & Absorption Kinetics**: The fraction absorbed is severely limited, and the predicted absorption rate ratio of 0.341 further indicates an underprediction in the absorption rate. Active efflux driven by P-gp appears to significantly restrict absorption, suggesting that the kinetic parameters of efflux transporters (Km and Vmax) might require re-optimization using data from different dose levels. Consideration should also be given to low passive permeability contributing to the low absorption extent.

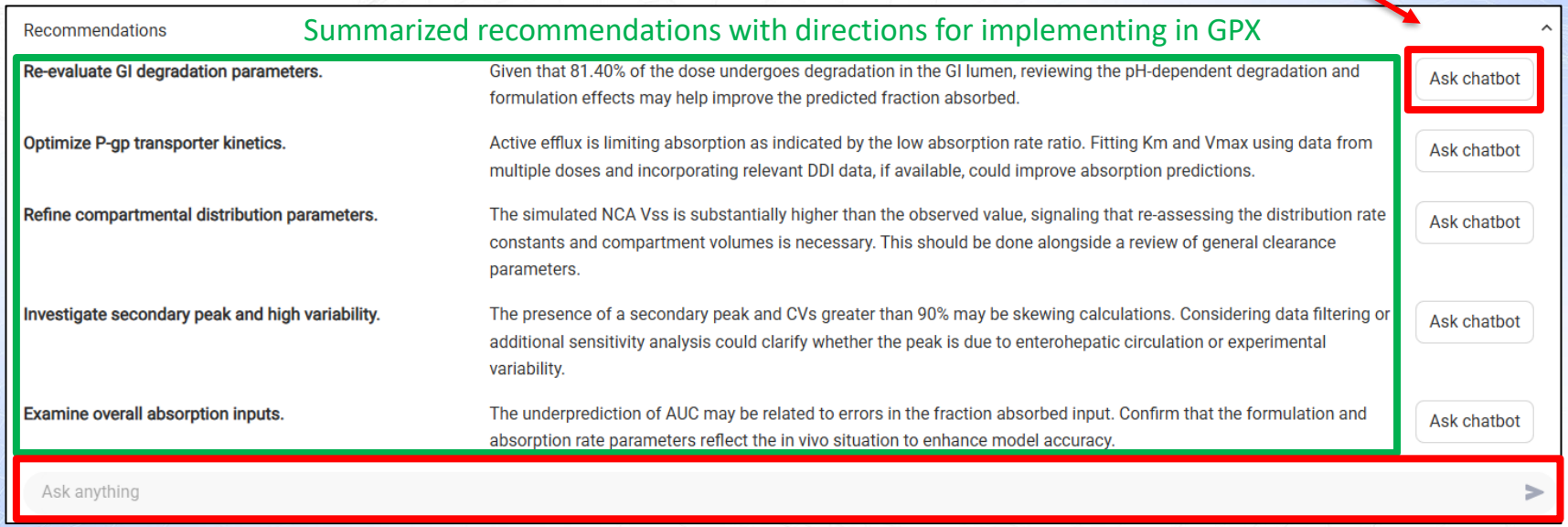




Plot generation is dynamic, depending on what processes occur in this particular simulation

AI Recommendations Bring it All Together

Ask the chatbot for more detailed instructions on how to follow the recommendation…



…or just ask it anything about your simulation and assessment

Recommendations

Explain how to perform the recommendation:
Re-evaluate GI degradation parameters.
with an associated rationale:
Given that 81.40% of the dose undergoes degradation in the GI lumen, reviewing the pH-dependent degradation and formulation effects may help improve the predicted fraction absorbed.
in GastroPlus.

To optimize the prediction of the absorbed fraction (Fa) in GastroPlus for your scenario—where 81.40% of the dose is lost to GI lumen degradation—focus on the following steps for re-evaluating gastrointestinal degradation parameters, with particular attention to pH-dependent degradation and formulation effects:

1. Review and Refine Degradation Model Inputs

- **Degradation Model Selection:**
  Ensure the appropriate degradation model is selected in GastroPlus. The model can be set to "None," "Rate," or "Half-life." For pH-dependent degradation, use the "Rate" or "Half-life" model and provide a table of degradation rates or half-lives as a function of pH.
  $\text{Degradation rate (k)} = f(\text{pH})$ This allows the model to interpolate degradation kinetics across the GI tract based on local pH values. *Source: Explicit guidelines for GPX*

- **Input Accurate Experimental Data:**
  Use measured degradation rates or half-lives at relevant pH values (e.g., stomach, duodenum, jejunum, ileum, colon). If available, include data reflecting the presence of excipients or formulation-specific effects on stability. *Source: GastroPlus Documentation : Lumenal Degradation*

2. Assess and Adjust pH-Dependent Degradation

What is the Fa in this simulation, and what contributes to it?

Fraction Absorbed (Fa) in This Simulation

Fraction absorbed (Fa):
In this simulation for oral Metoprolol Tartrate, the predicted Fa is **15.65%**. This means that only 15.65% of the administered dose is absorbed across the gastrointestinal (GI) epithelium into the enterocytes.

Factors Influencing Fa in This Simulation

The value of Fa is determined by several mechanistic and formulation-related factors, which in this case are:

1. GI Luminal Degradation

- **81.40%** of the dose is lost to chemical degradation in the GI lumen before absorption can occur.
- This is the primary limiting factor for Fa in this simulation.
- Degradation is likely pH-dependent and may be influenced by formulation excipients or microenvironmental pH.

2. Efflux Transport (P-gp)

- Active efflux via P-glycoprotein (P-gp) significantly restricts absorption.
- The simulation notes that optimizing P-gp kinetic parameters (Km, Vmax) could improve Fa.
- Efflux transporters can pump drug back into the lumen, reducing net absorption.

3. Passive Permeability

- Low passive permeability may further limit the extent of absorption.
- Only dissolved drug is available for absorption; permeability is a function of drug properties and GI physiology.

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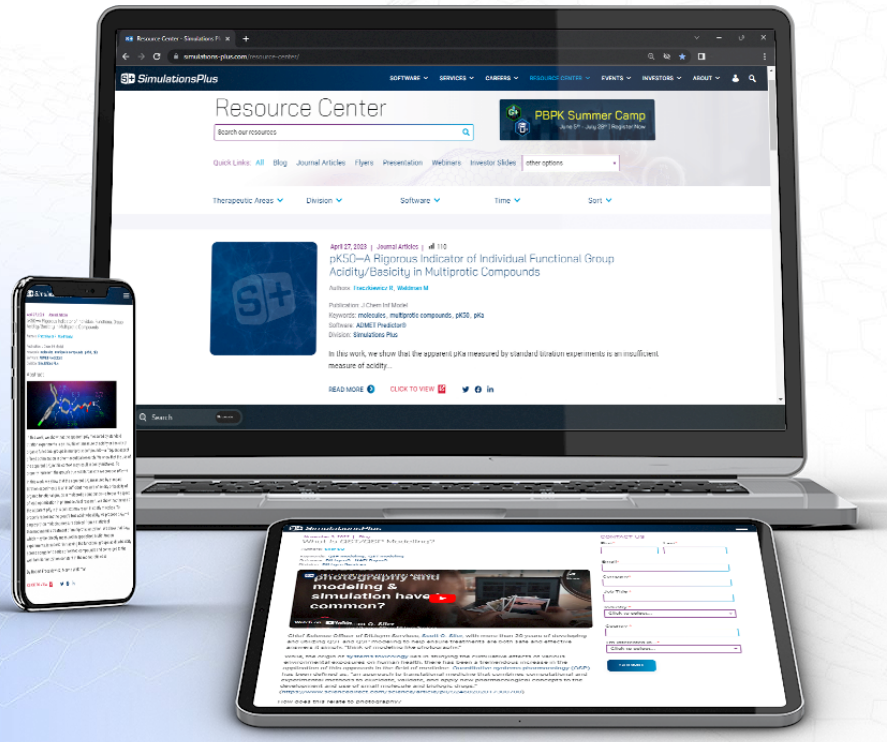

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