



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

Anant Ketkar

Principal Scientist and Scientific Lead – India
Physiologically Based Pharmacokinetic (PBPK) Solutions

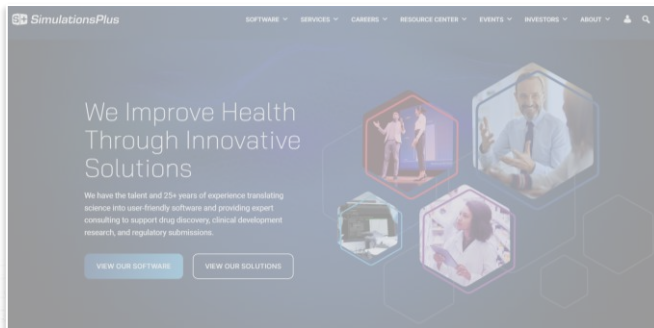
One-Day National Seminar on "AI in Pharmaceutical Development"
@NGSM Institute of Pharmaceutical Sciences, Mangalore

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.



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.

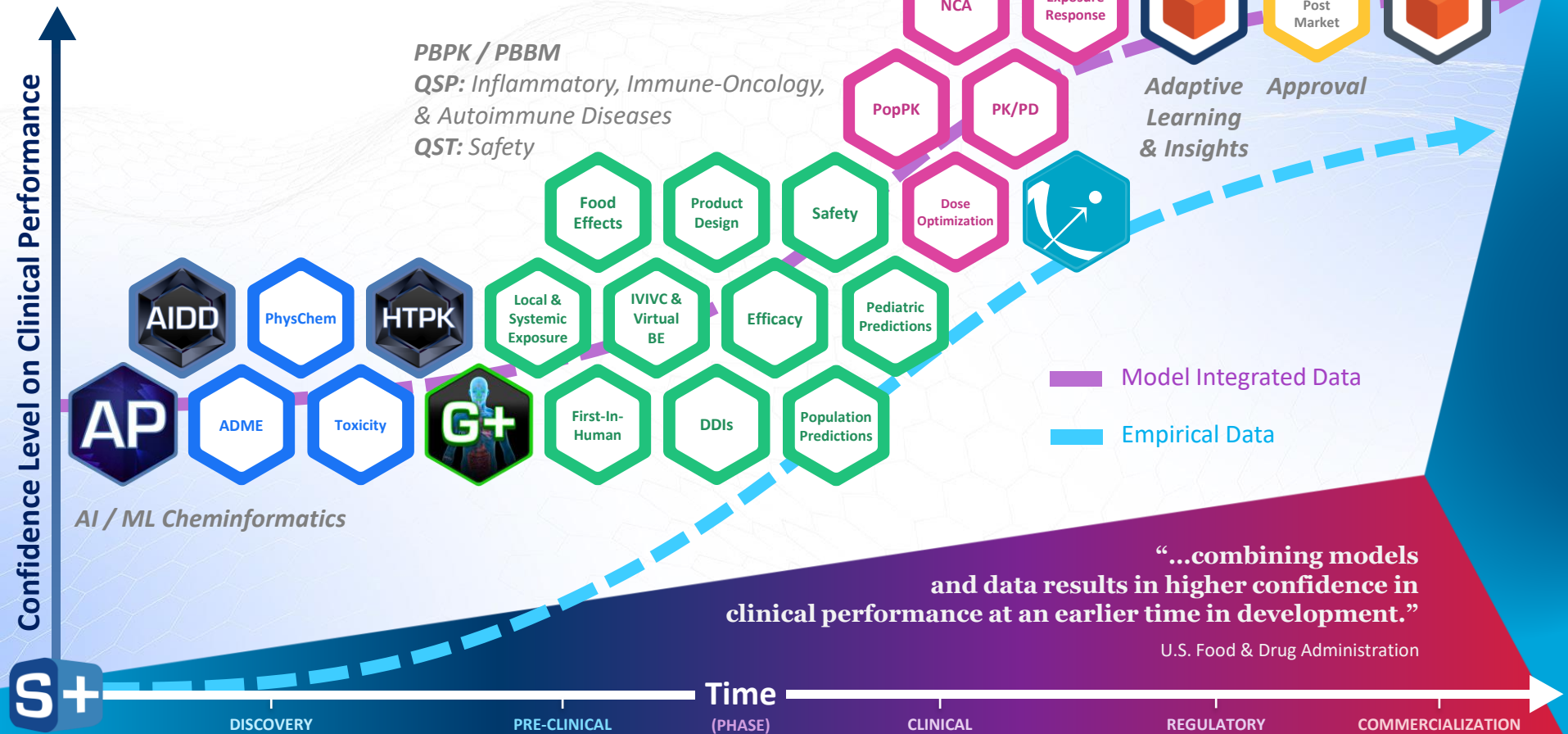
Established
In 1996

Complementary Solutions

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

Clinical Pharmacology & Pharmacometrics

Medical Communications



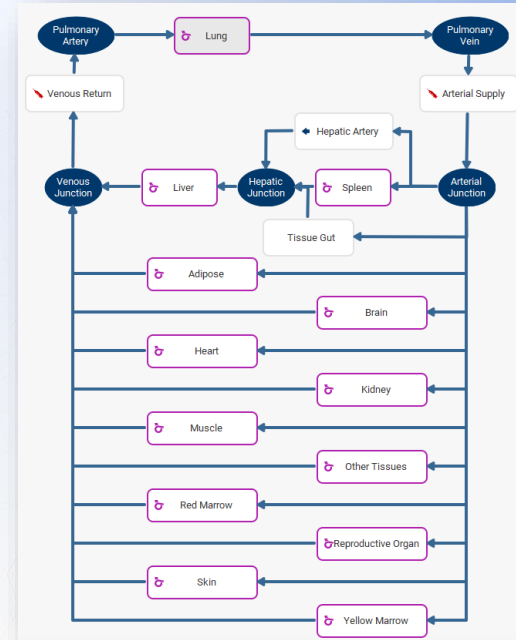
Definitions and Context

PBPK M&S and PBBM

- **PBPK Modelling: Physiologically Based Pharmacokinetic 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: Physiologically Based Biopharmaceutics Modelling**
 - 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® ACAT
Model Structure**

Compartment	Permeability (cm/s)	ASF (1/cm)	f_{loss}	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

**GastroPlus® PBPK
Model Structure**

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>



 13 December 2018 EMA/CHMP/VAS/5101/2016 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 2018
Draft agreed by Pharmacokinetics Working Party	May 2018
Adopted by CHMP for release for consultation	21 July 2018
Start of public consultation	29 July 2018
End of consultation (deadline for comments)	31 January 2019
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019
Keywords	pharmacokinetics, modelling, simulation, qualification, predictive performance

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



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>



Guidelines for Analysis Reports Involving Physiologically Based Pharmacokinetic Models

In recent years, much attention is being given to drug development strategies that use modeling and 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., pediatric), and determining dosage and regimen.

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

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

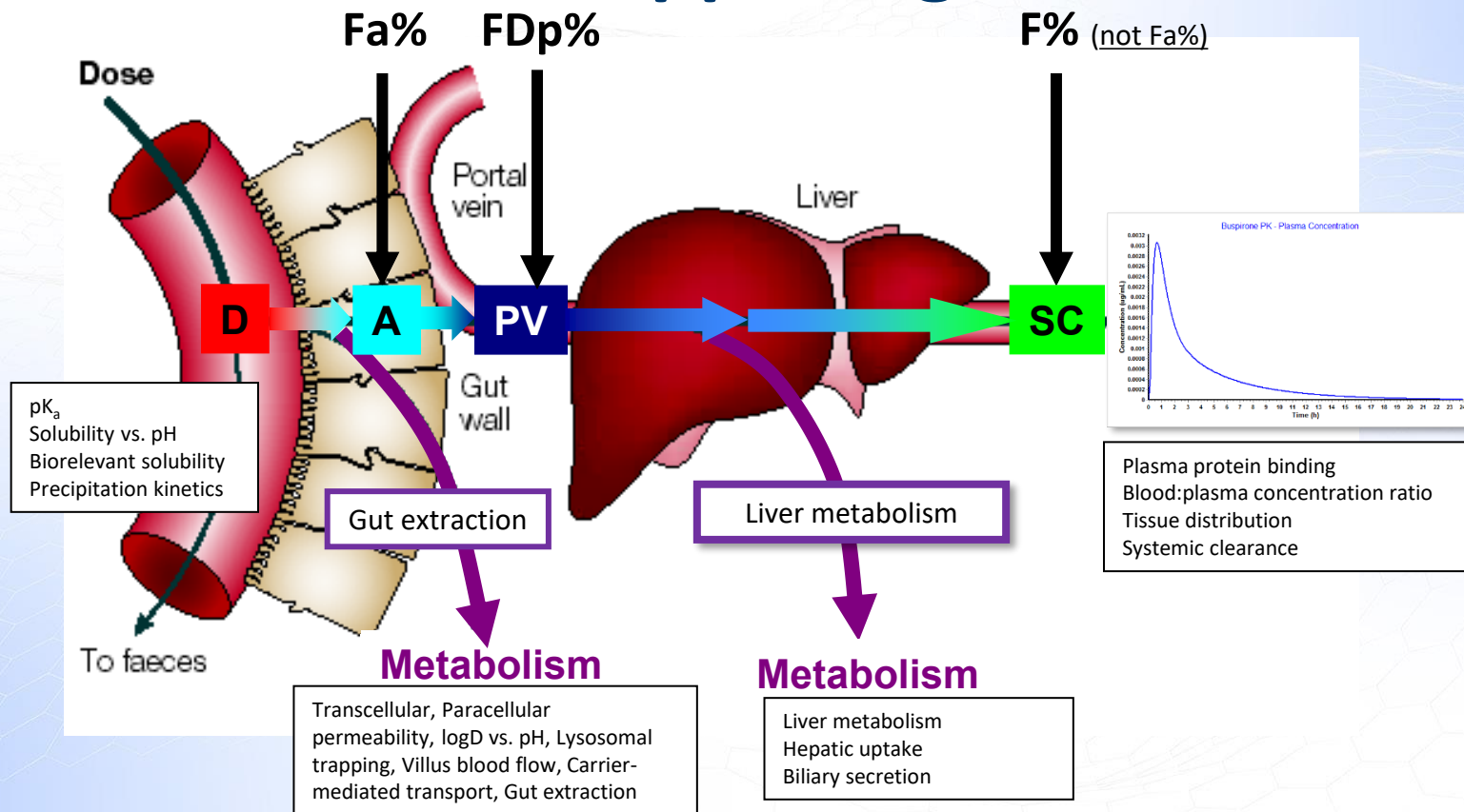
<https://www.pmda.go.jp/files/000239317.pdf>



GastroPlus® and an Overview of Mechanistic Processes

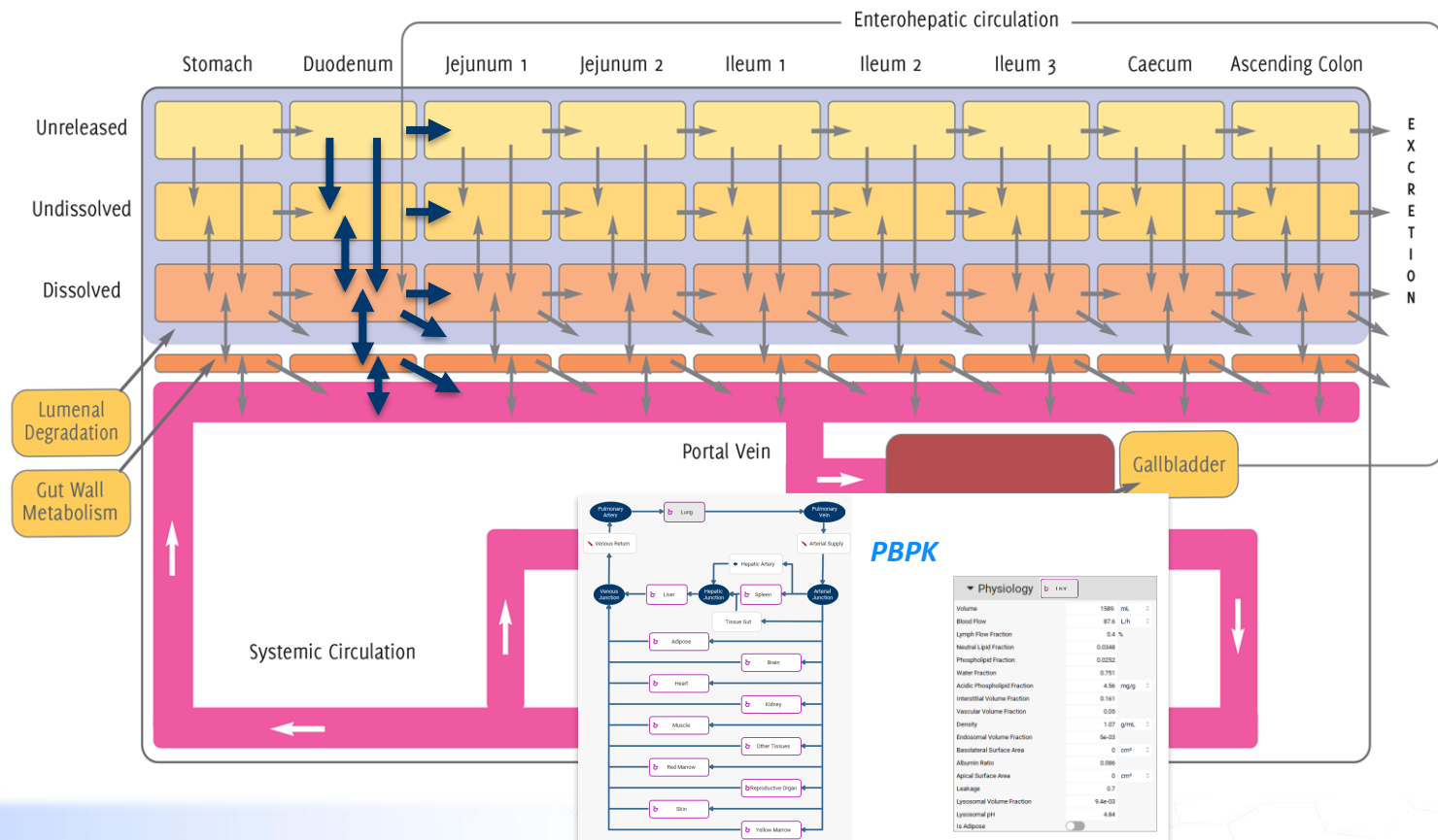
Oral Absorption Modelling

What is happening *in-vivo*?

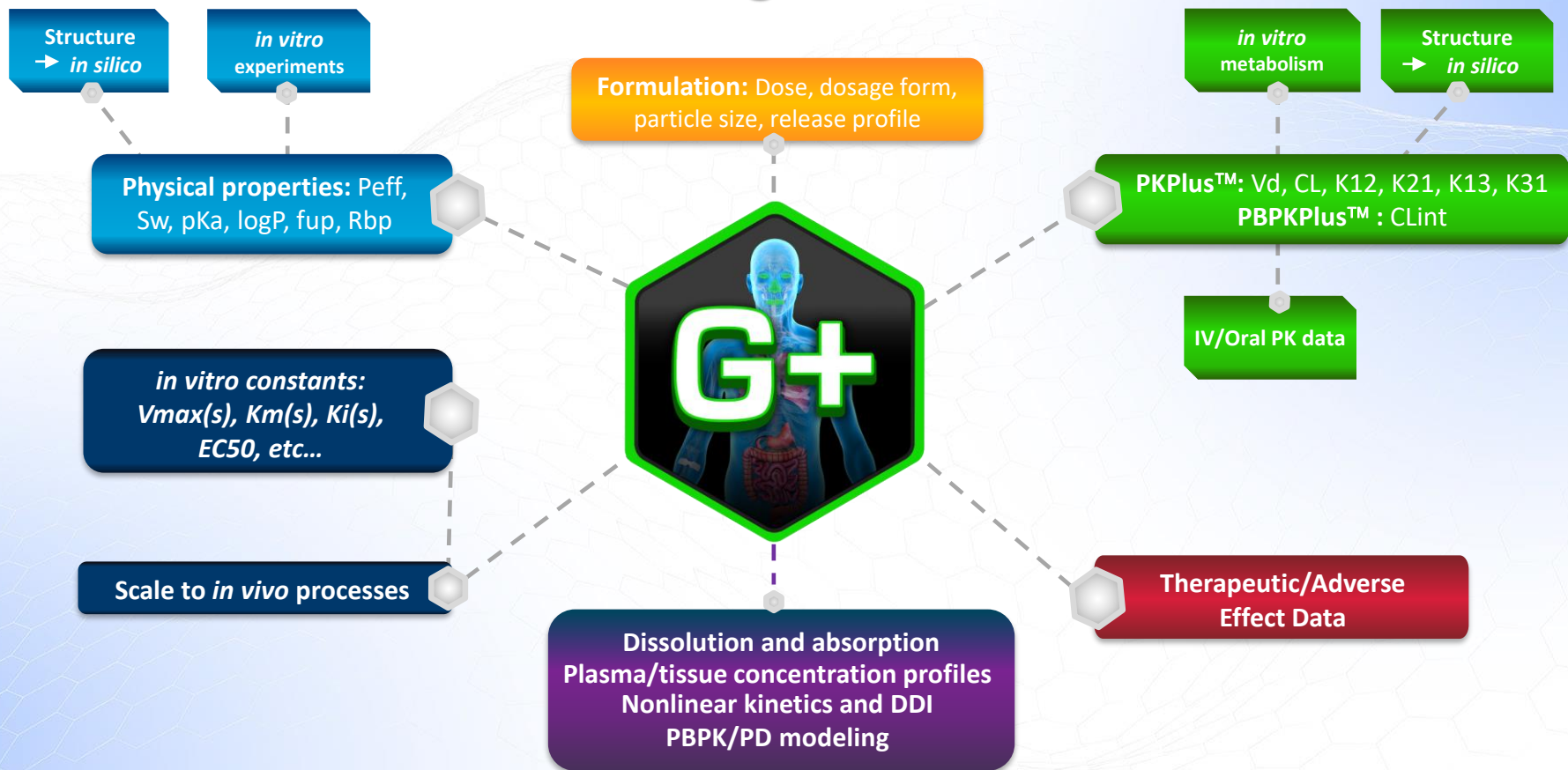


* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

Advanced Compartmental Absorption and Transit Model (ACAT™)

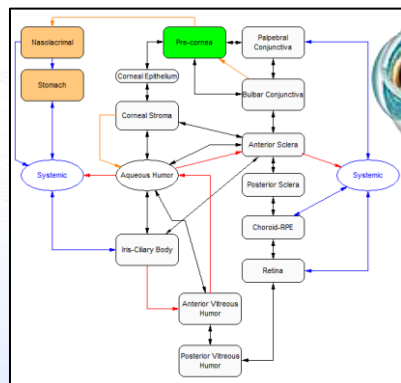


The Big Picture



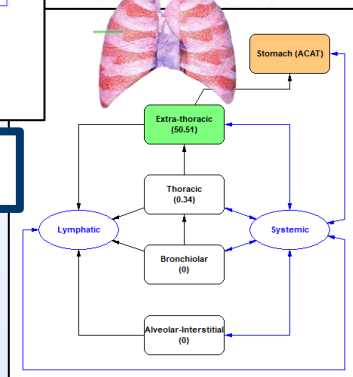
Pathways Beyond Oral Absorption...

Ocular (OCAT™)



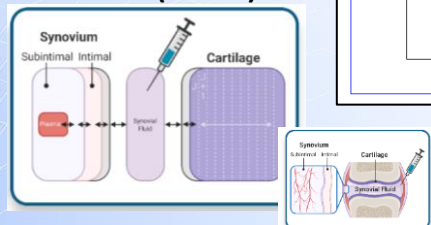
FDA: Ocular model extensions

Pulmonary (PCAT™)



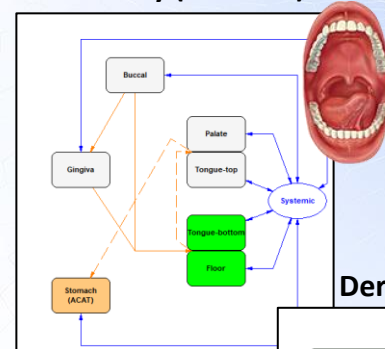
FDA: Pulmonary model extensions

Intraarticular (ICAT™)



FDA: Long-acting injection model extensions

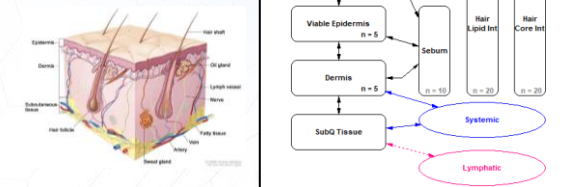
Oral Cavity (OCCAT™)



FDA: Oral cavity model extensions

Dermal (TCAT™)

FDA: Dermal model extensions

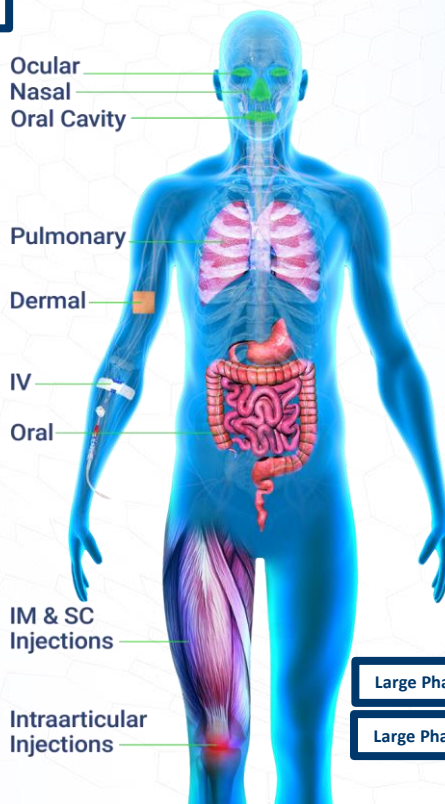


Large Pharma: ACAT™ model extensions

Large Pharma: Local GI disease extensions

FDA: Oral absorption model extensions

Large Pharma: Virtual BE trial simulator

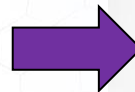
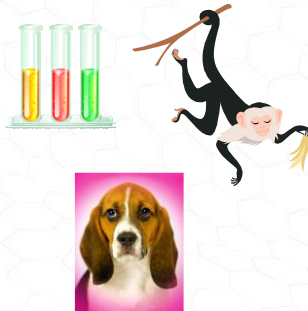
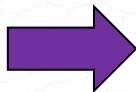
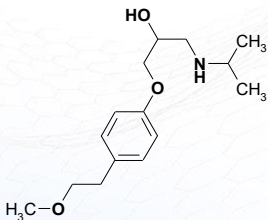


Where is GastroPlus® Being Used Today?

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

The screenshot displays the GastroPlus software interface. The left sidebar contains a **Navigation Pane** with menu items: Dashboard, Observed Data, Compounds, Dosing, Physiologies, Pharmacokinetics, Physiology Schedules, Simulations, Runs, Analysis, and Lab Book. The top bar includes a **Messages** section with tabs for Level, Clear, View, and Panel, and a **Project: test** indicator. The main area is the **Message Center**, which is currently showing the **Compounds View**. This view includes a table for **Molecular Properties** with a sub-panel for **Solubility**. The **Solubility** sub-panel contains a table with columns: Form Name, Solubility (mg/mL), pH, Temperature (°C), Intrinsic Solubility, Density (g/mL), Estimate Tension, Interfacial Tension (J/m²), and Use For Precipitation. The table has one row for **Form 1** with values: 1, 7, 37, a toggle switch, 1.2, a toggle switch, 0, and a toggle switch. Below the table are buttons for Add, Copy, Delete, and Calc. Native pH. The right sidebar is the **Modules** pane, listing ADMET Predictor®, DDI, IVIVCPlus™, Metabolism & Transport, PBPKPlus™, PDPlus™, and PKPlus™. The **Navigation Pane**, **Message Center**, and **Modules** pane are highlighted with yellow boxes. The **Compounds View** area is highlighted with a red box. The **Solubility** sub-panel is highlighted with a blue box. The **Biorelevant In Vitro Solubilities** sub-panel is highlighted with a blue box.

Navigation Pane

Message Center

Compounds View

Molecular Properties

Solubility

Form Name	Solubility (mg/mL)	pH	Temperature (°C)	Intrinsic Solubility	Density (g/mL)	Estimate Tension	Interfacial Tension (J/m²)	Use For Precipitation
Form 1	1	7	37	<input type="checkbox"/>	1.2	<input type="checkbox"/>	0	<input checked="" type="checkbox"/>

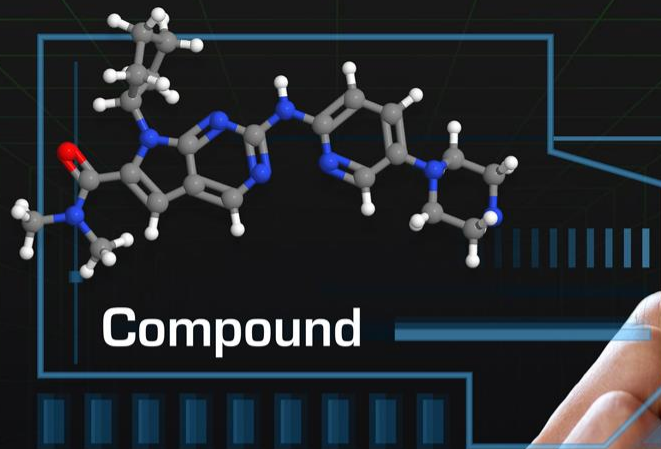
Panel

Subpanel

Modules

Modules Pane

What goes into a simulation?



Formulation

Pharmacokinetics

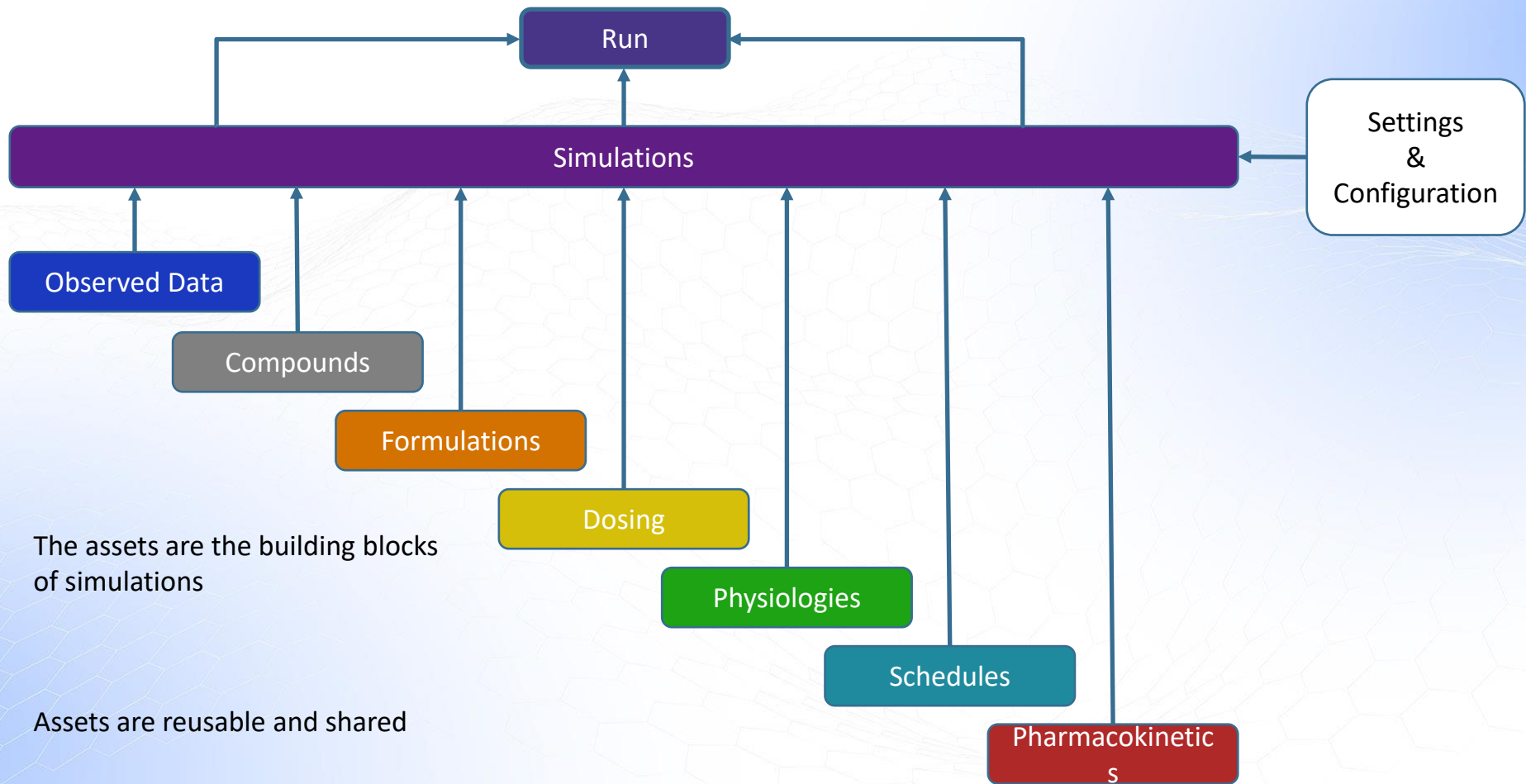
Absorption
Distribution
Metabolism
Elimination

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 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 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 fast mal PBPK perf

Compound X enz

Tablet

Tablet 50 mg

PBPK perf

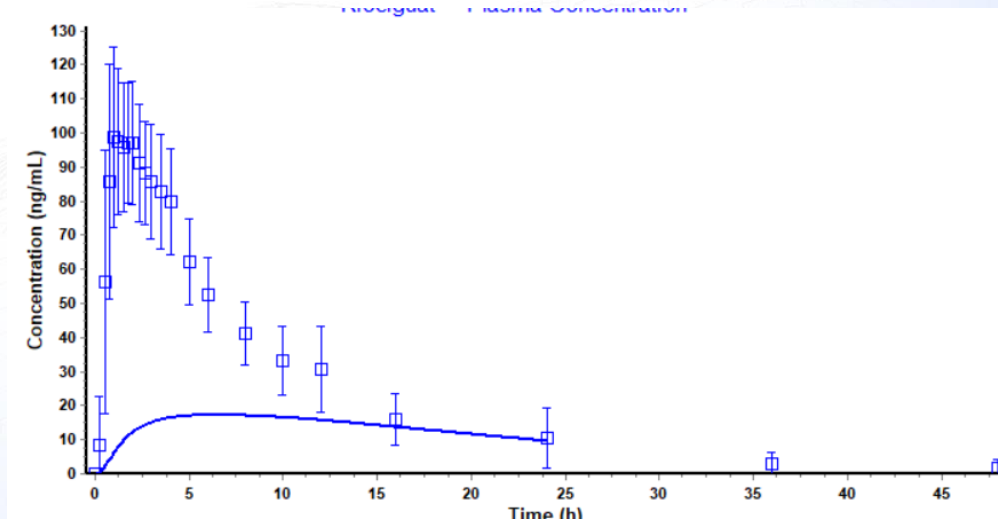
Fast HumMal75kg

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

Assessment

Assessments SimAssessment1 ▾ Add Rename Copy Delete

▼ Simulation Assessment

Simulation Type PO ▾

Simulation Midazolam15mg NoGFJ ▾

Mode Improve Fit to Observed Data ▾

Scenario Fit Model to PO Data ▾

Oral Cp-time data is available. Improve the fit of the simulated profile to the observed data.

Compare to ADMET Predictor ☐

ADMET Predictor file path Select File

Comparator ▾





Assess

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

Click to run the assessment

Assess				
Level	Clear	Topic	Feedback Type	Description
Information	Done	Summary	Descriptive	This is a Compartmental simulation for 15.00 mg of Midazolam administered orally.
Information	Done	Summary	Descriptive	The simulated NCA Cmax is: 136.74 ng/mL. The simulated NCA Tmax is: 2.23 h. The simulated NCA AUC0-t is: 1.09e+3 (ng/mL)·h.
Information	Done	Summary	Descriptive	The Fa is: 1.00. The Fdp is: 1.00, and the Fg is: 1.00. The Fh is: 1.00, and the F is: 1.00.
Information	Done	Summary	Descriptive	The NCA Vss for the full simulated profile is: 92.01 L. The NCA CL for the full simulated profile is: 13.53 L/h. The NCA Kel for the full simulated profile is: 0.183 1/h.
Information	Done	Summary	Descriptive	The observed NCA Vss is: 585.82 L. The observed NCA CL is: 82.77 L/h. The observed NCA Kel is: 0.0779 1/h.
Information	Done	Observed Exposure Summary	Descriptive	The observed NCA Cmax is: 48.33 ng/mL. The observed NCA Tmax is: 0.670 h. The observed NCA AUC0-t is: 165.62 (ng/mL)·h.
Information	Done	Distribution	Descriptive	This simulation uses a Two compartment model for Midazolam. The apparent Vss of Midazolam by NCA is 92.01 L.
Information	Done	Overall Clearance	Descriptive	The total mass of drug cleared by the end of the simulation is 14.75 mg, which is 98.36 % of the administered dose, and 98.36 % of the amount that is absorbed.
Information	Done	Overall Clearance	Descriptive	This includes 0 mg via liver enzymes and 14.75 mg via systemic linear pathways (with 0 % being further cleared into bile via Biliary Clearance Fraction).
Information	Done	Renal Clearance	Descriptive	No relevant feedback for Simulation Renal Clearance
Information	Done	Biliary Clearance	Descriptive	No biliary elimination is occurring in this simulation.
Information	Done	Metabolic Clearance	Descriptive	No metabolism is occurring in this simulation.
Information	Done	Linear Clearance	Descriptive	14.75 mg of Midazolam is cleared via general compartmental clearance in this simulation. This equates to 98.36 % of the dose, and 100.00 % of the total mass cleared. The rate of general clearance in this simulation is 13.65 L/h.
Information	Done	Observed Clearance	Descriptive	There is no clearance mapped in the observed data.
Information	Done	Controlled Release	Descriptive	No relevant feedback for Simulation Release
Information	Done	Precipitation	Descriptive	Midazolam is not predicted to precipitate in this simulation.

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



GastroPlusChat

AssessmentsPlus™ AI

Data Extractor

Select the
AssessmentsPlus AI
application

GastroPlusChat

Questions answered using GastroPlusX documentation and tutorials.

How can you use GPX to compare the pharmacokinetic profiles of different formulations for the same compound?

What challenges might you encounter when modeling highly permeable compounds in GPX?

What are the main differences between PBPK and compartmental PK modeling in GPX?

Ask anything



Can also upload saved results

Input

Choose input method

☒ Upload JSON file ☐ Paste JSON content

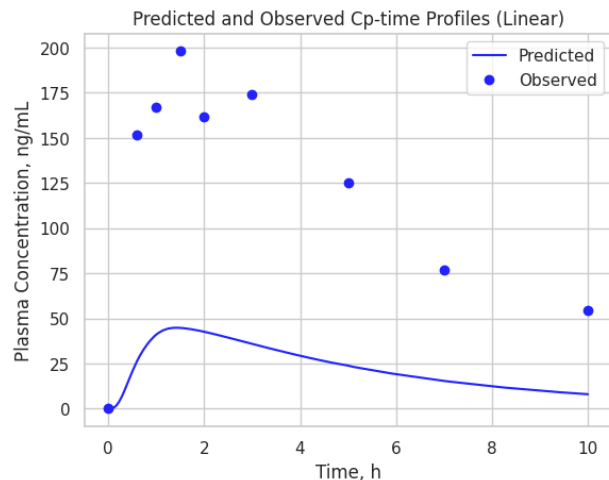
Paste your JSON content here

```
{
  "Feedback Type": "Actionable",
  "Topic": "Simulated vs. Observed Distribution",
  "Level": "Information",
  "Confidence": "Unknown",
  "Feedback": "The volume of distribution and rate of clearance entered in the model appear to be appropriate. As AUC is overpredicted for this oral simulation, consider if FPE is missing from the model, or if the amount of drug absorbed is too high. ",
  "Tags": [],
  "Assessment Plot Datas": [],
  "Assessment Plot Tables": [],
  "Additional GPT Instructions": []
},
{
  "Feedback Type": "Actionable",
  "Topic": "Precipitation",
  "Level": "Information",
  "Confidence": "Unknown",
  "Feedback": "Since your compound type is a base that may precipitate upon entry in the intestine, have you checked that the drug is able to supersaturate at the dose of 15.00 mg using for example a pH-shift experiment and whether the parameterization of precipitation could improve your simulation. Ideally, if there is precipitation, we recommend you use a mechanistic precipitation model and verify its parameters using preclinical and clinical data at various doses or prandial states. ",
  "Tags": [],
  "Assessment Plot Datas": [],
  "Assessment Plot Tables": [],
  "Additional GPT Instructions": []
},
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  "Feedback Type": "Actionable",
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  "Level": "Information",
  "Confidence": "Unknown",
  "Feedback": "In addition, there could be luminal degradation of your drug due to pH or microbiota which was not included in the model. Check for potential drug luminal degradation. If the simulation is reproducing a DDI scenario, check that the induction or inhibition or chemical interaction were well parameterized. ",
  "Tags": [],
  "Assessment Plot Datas": [],
  "Assessment Plot Tables": [],
  "Additional GPT Instructions": []
},
{
  "Feedback Type": "Actionable",
  "Topic": "Dissolution",
  "Level": "Information",
  "Confidence": "Unknown",
  "Feedback": "In addition, the input parameters of your simulation indicate that there is little solubility limitation to the absorption. Can you check if the solubility vs pH profile and effect of bile salt has been adequately parameterized? Check your aqueous pH solubility profile against Henderson Hasselbalch equations, the impact of micro-environmental pH and use measured biorelevant solubility values to calculate the effect of bile salts on solubility and dissolution rate. ",
  "Tags": [],
  "Assessment Plot Datas": [],
  "Assessment Plot Tables": [],
  "Additional GPT Instructions": []
}
}
```

Run assessment

Click to run the AI enhancement

- 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 C_{max} and AUC_{0-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.

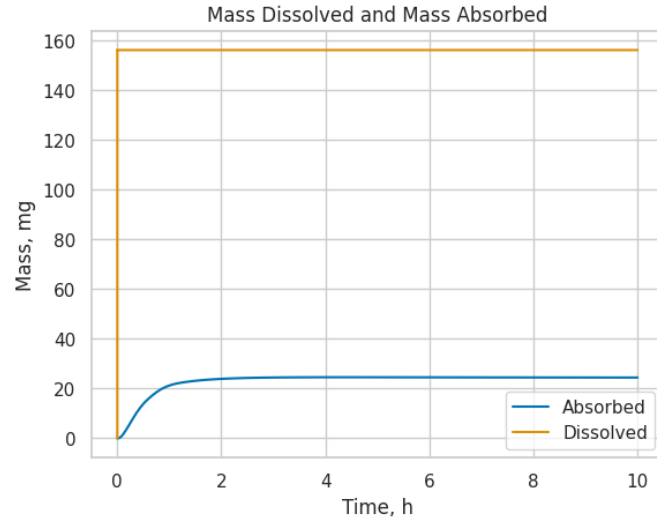
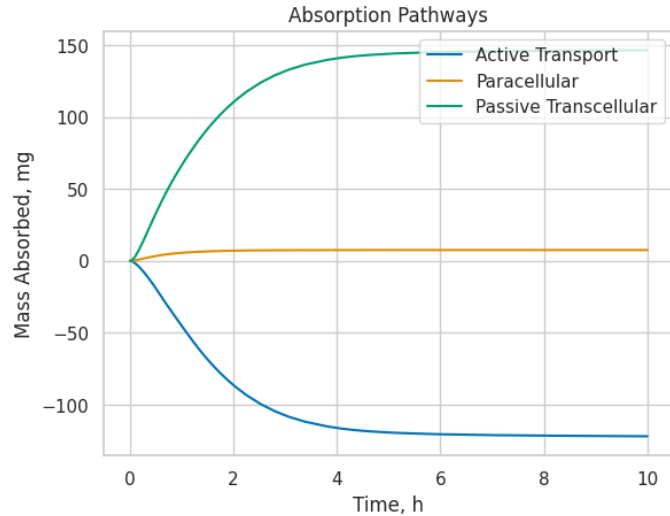
- Executive Summary:** The simulation of oral Metoprolol Tartrate using a compartmental model exhibits clear discrepancies with the observed data, notably in exposure (AUC) and predicted pharmacokinetic parameters. There is a significant underprediction of AUC and peak concentrations, along with overpredicted 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.

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- **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 (K_m and V_{max}) 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...

Recommendations

Summarized recommendations with directions for implementing in GPX

Re-evaluate GI degradation parameters.	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.	Ask chatbot
Optimize P-gp transporter kinetics.	Active efflux is limiting absorption as indicated by the low absorption rate ratio. Fitting K_m and V_{max} using data from multiple doses and incorporating relevant DDI data, if available, could improve absorption predictions.	Ask chatbot
Refine compartmental distribution parameters.	The simulated NCA V_{ss} is substantially higher than the observed value, signaling that re-assessing the distribution rate constants and compartment volumes is necessary. This should be done alongside a review of general clearance parameters.	Ask chatbot
Investigate secondary peak and high variability.	The presence of a secondary peak and CVs greater than 90% may be skewing calculations. Considering data filtering or additional sensitivity analysis could clarify whether the peak is due to enterohepatic circulation or experimental variability.	Ask chatbot
Examine overall absorption inputs.	The underprediction of AUC may be related to errors in the fraction absorbed input. Confirm that the formulation and absorption rate parameters reflect the in vivo situation to enhance model accuracy.	Ask chatbot

Ask anything

...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 (F_a) 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.

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 F_a in this simulation, and what contributes to it?



Fraction Absorbed (F_a) in This Simulation

Fraction absorbed (F_a):

In this simulation for oral Metoprolol Tartrate, the predicted F_a 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 F_a in This Simulation

The value of F_a 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 F_a 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 (K_m , V_{max}) could improve F_a .
- 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.



For More Information:

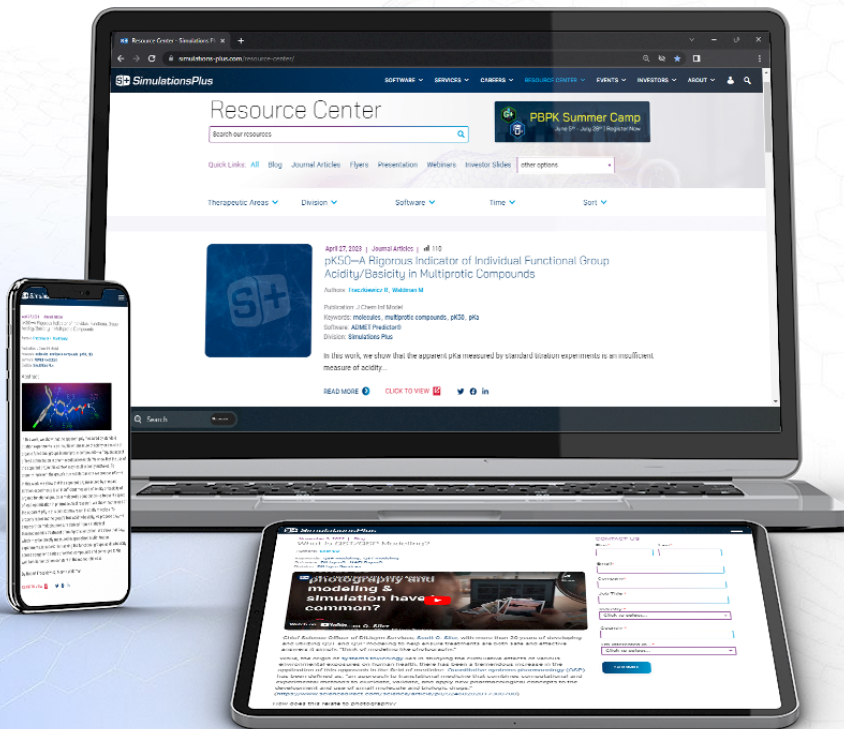
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