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GastroPlus® 9.8

Validating more than just your 'gut instinct'

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GastroPlus® 9.8

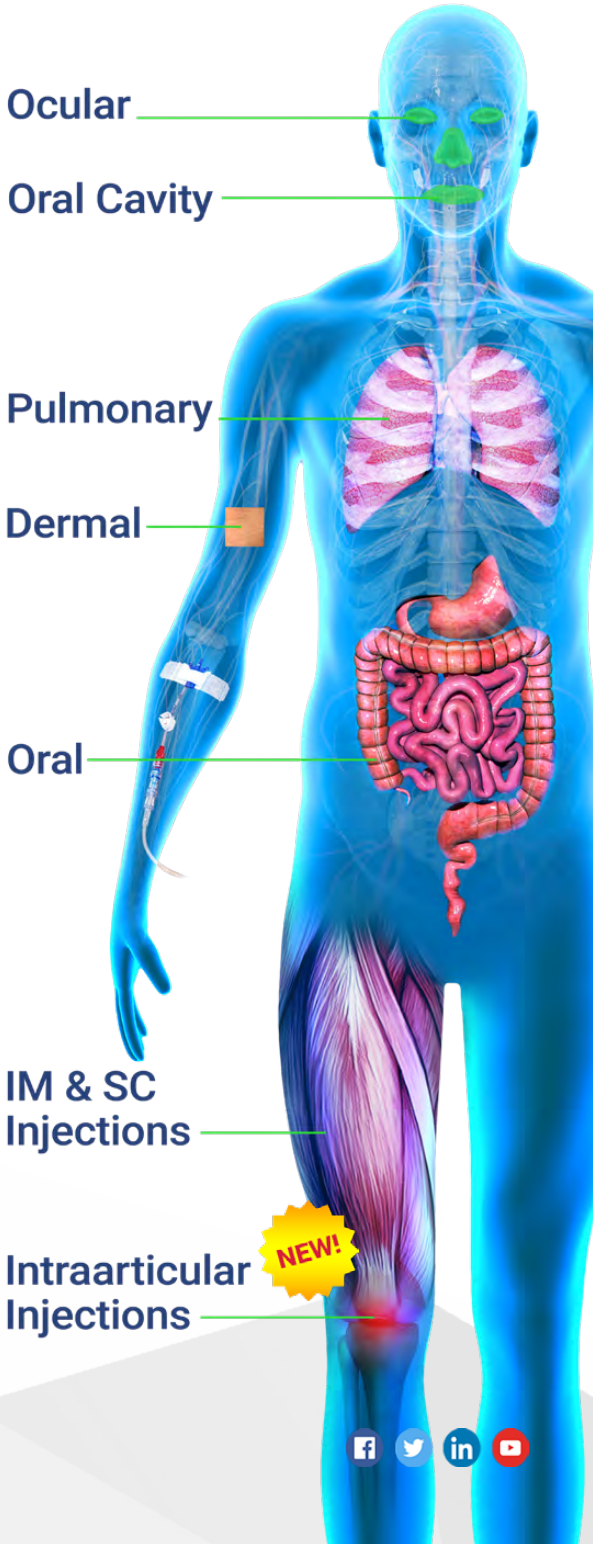
Validating more than just your 'gut instinct'

PBBM PBPK modeling software... to support research & regulatory submissions

GastroPlus is a mechanistically based, validated software package that simulates absorption, pharmacokinetics, pharmacodyanmics, and DDIs in human and animal populations.

What's new in version 9.8?

- **SPECIAL FOCUS ON VIRTUAL BIOEQUIVALENCE:** Updated physiological CV% for gut parameters, automated execution of repeated trials & crossover studies; intra subject variability - packaged within a user friendly interface. This powerful BE trial simulator will accelerate the evaluation of biowaiver requests - for both oral and non-oral products
- **NEW!** Additional Dosage Route model; Intraarticular injections
- **NEW!** Machine learning models for transporter & clearance endpoints in the ADMET Predictor® Module.
- **UPDATED & NEW!** Validated DDI standard models
- **Large pharma collaboration:** Long Acting Injectable model extensions for IM/SC dosing routes
- **Large pharma collaboration:** Pulmonary PBPK model (PCAT™) extensions - simulation of volatile compounds & lysosomal trapping considerations
- **Large pharma collaboration:** Systemic PBPK lung model extensions
- **FDA collaboration:** Ocular model (OCAT™) extensions including; protein binding in individual tissues & topical ointment formulation
- **ENHANCEMENTS!** to the top-ranked ACAT™ model
- **NEW!** Non-pharma collaboration: Transdermal model (TCAT™) model extensions



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Rev. 12/29/2020

ADMET Predictor® Module

CYP metabolism predictions from chemical structure – quickly create full PBPK models in seconds.

The ADMET Predictor Module extends the capability of GastroPlus by enabling you to obtain predictions from structure of all physicochemical, pharmacokinetic, and CYP metabolism kinetic parameters required for GastroPlus PBPK simulations. The module uses the same models as our best-in-class ADMET Predictor software.

Enhanced pKa model developed in collaboration with **Bayer HealthCare** - ALL models retrained with greater accuracy!

This module automatically generates predictions for the following properties:

- CYP metabolism kinetics – Vmax, Km, and CLint
- P-gp and OATP transporter inhibition models (classification)
- Aqueous solubility vs. pH profile
- Biorelevant solubility (FaSSIF, FeSSIF, and FaSSGF)
- logD vs. pH profile
- Rabbit corneal permeability
- Human volume of distribution
- Blood:brain barrier permeation (classification)
- pKa(s)
    - Tendency to supersaturate in water
    - Diffusion coefficient in water
- Human effective permeability
    - Human plasma protein binding
    - Human blood:plasma concentration ratio

The ADMET Predictor Module has several critical benefits:

1. by loading a library of chemical structures, you can quickly set up a database for screening fraction absorbed & bioavailability – decide which compounds to carry forward into *in vivo* studies
2. use the *in silico* predictions and Parameter Sensitivity Analysis to guide your *in vitro* studies
3. begin evaluating different formulation strategies to assess the importance of factors like particle size, solubility and dose on absorption

Drug-Drug Interaction (DDI) Module

The DDI Module in GastroPlus allows you to predict drug-drug interactions (DDIs) among drugs and metabolites.

The ability to accurately estimate potential DDIs *in silico* has several benefits for companies:

- Explore possible effects on the pharmacology and toxicology of drugs
- Identify species-specific changes to estimate how a drug behaves in animals vs. humans
- Investigate the safety profile of drugs that are co-administered prior to filing regulatory submissions with agencies around the world

With the DDI Module, calculating either steady-state and/or dynamic DDIs is managed through our easy-to-use interface. We provide a database of standard compounds for which all relevant parameters (including reported inhibition/induction constants and full compartmental PK/PBPK models) are defined. Of course, you may predict DDIs among any compounds by simply entering the required inputs. As with other GastroPlus modules, there is no equation or code writing required.

What are some of the advantages to using the DDI Module?

- Models of standard compounds (substrates/inhibitors inducers)
- PBPK models for DDI standard compounds
- Population Simulator™ linked with DDI predictions
- Transporter-based drug-drug interactions
- Metabolic and/or transporter induction
- Linked with the industry's #1-ranked dissolution/absorption (ACAT™) model
- Use with either compartmental PK or PBPK models
- Apply competitive and/or time-dependent inhibition kinetics by parent and/or metabolite(s)
- Simulate DDIs for any species
- Account for enzyme expression level differences in various human populations
- Built-in tool to easily calculate the fraction metabolized (fm) from *in vitro* assays (rCYPs and microsomes are accommodated)
- Incorporate nonlinear gut contributions to DDIs
- Predict the inhibitor effect using simulated concentrations at the site of metabolism (gut, liver, or any PBPK tissue) for dynamic DDI simulations
- Include the effects of multiple substrates on clearance of other substrates metabolized by the same enzyme

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PBPKPlus™ Module

Ranked #1 in *in vitro-in vivo* Extrapolation (IVIVE) by Pfizer!
(Cole et al., 2nd Asian Pacific Regional ISSX Meeting, May 2008, Shanghai, China)

Only in GastroPlus! Transporter-based IVIVE: automated scaling of permeability across tissues in the PBPK model

The PBPKPlus Module extends GastroPlus to define a "whole body" PK model, consisting of various tissues. You can easily simulate the distribution & elimination of compound throughout the body and track concentrations in any tissue. Tissues can be defined as needed, or default models can be used with a standard set of compartments:

- Adipose
- Arterial blood
- Brain
- Yellow marrow
- Gut
- Heart
- Lungs
- Kidney
- Liver
- Muscle
- Skin
- Red marrow
- Spleen
- Reproductive organs
- Venous blood

Ability to add lysosomal trapping effect to PBPK tissues

Customize your PBPK model by treating any tissue as either a perfusion-limited or permeability-limited model, and quickly add/delete tissues as needed – all without writing any equations!

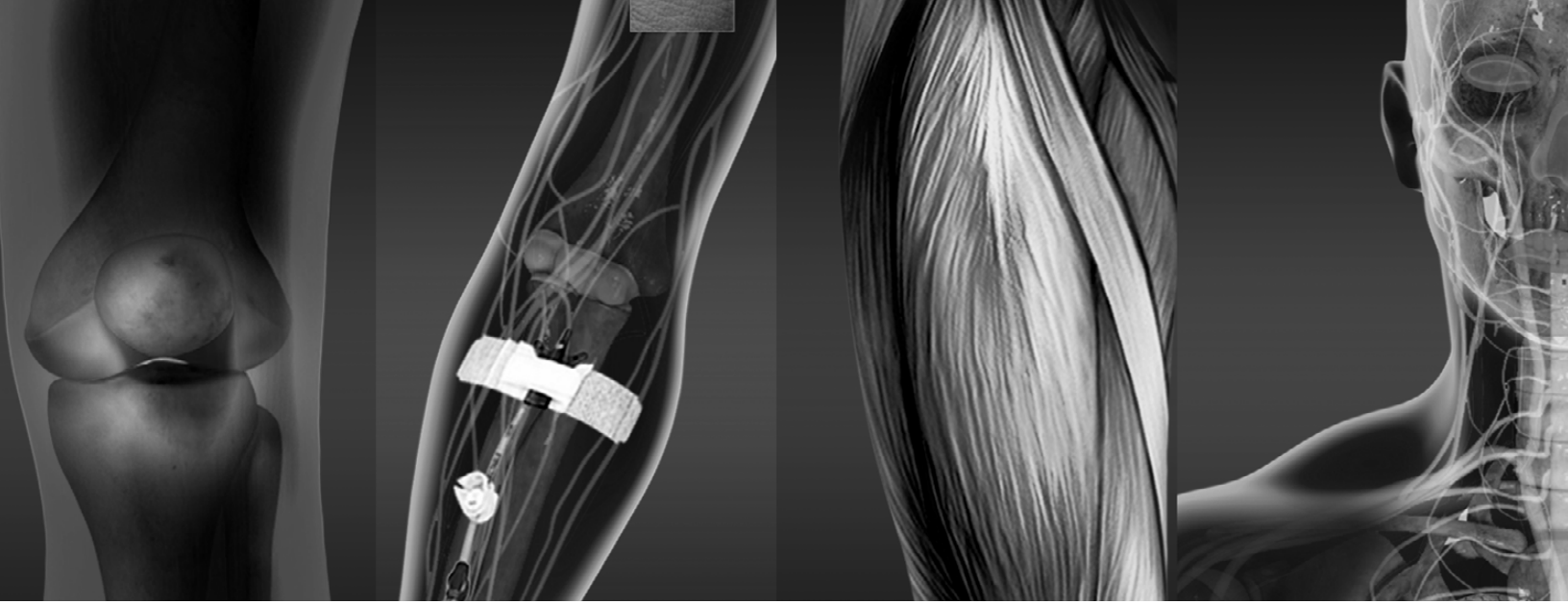
The PBPKPlus Module also provides:

- Generation of physiological model parameters (tissue weights and volumes, composition, perfusion rates, etc…) with our built-in PEAR Physiology™ (Population Estimates for Age-Related Physiology).

Current physiologies are:

- Mechanistic pregnancy PBPK model (with fetus compartment)
- Human (American, Japanese, and Chinese, Male or Female, based on age)
- Infant/pediatric groups
- Hepatic impairment
- Renal impairment
- Obesity
- Rat
- Dog
- Mouse
- Monkey
- Rabbit
- Minipig

- Population simulations based on parameter variances in a sample population – define your own age range, % male vs. female, and the number of "virtual" subjects you wish to create
- Novel methods for estimating tissue partition coefficients from logD, pKa, plasma protein binding and Rbp –only in GastroPlus!
- Physiological model for kidney including glomerular filtration and reabsorption
- Fitting models to *in vivo* data (plasma/tissue concentrations, amount excreted in urine, etc…)
- Linking of pharmacodynamic effect directly to concentrations in specific tissues
- Mechanistic transport of drug from hepatocytes to bile in liver, modeled either as a linear process or through carrier-mediated transport
- Report-quality plotted output of all time-dependent results in all tissues
- … and more!



Additional Dosage Routes Module

The Additional Dosage Routes Module in GastroPlus extends the program beyond the traditional oral and intravenous administration routes. With this module, you can simulate drug disposition through additional dosing sites – dermal, intraoral (oral cavity), ocular, pulmonary (intranasal and respiratory), and intramuscular. These models were all developed in collaboration with top 5 pharmaceutical companies. The ability to predict concentration profiles in different regions of the skin, mouth, eye, lungs, nose, and muscle can help you:

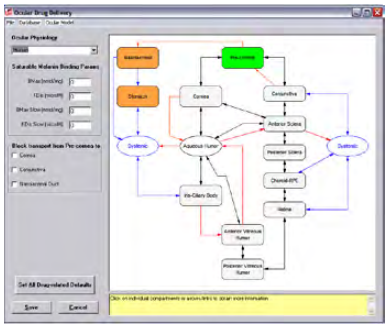
- Explore various formulation/drug delivery options to achieve desired therapeutic effects
- Identify species-specific changes to estimate how a drug is handled in animals vs. humans

With the Additional Dosage Routes Module, simulating concentrations through these sites is managed through our easy-to-use interface. Mechanistic, physiologically-based models are provided for each tissue, for different species. You can also customize your own physiology by entering available information into the program. These models are linked with either compartmental or physiologically-based pharmacokinetics (PBPK) in GastroPlus, so you may predict your drug's distribution and elimination once it enters into the systemic circulation. As with other GastroPlus modules, there is no equation or code writing required.

NEW! Intramuscular Injection Delivery Model!

Ocular Model (Ocular Compartmental Absorption & Transit (OCAT™) Model

- Nonlinear metabolism or transport in any eye tissue!
- Two-site melanin binding options!
- Convective flow incorporated into the ocular disposition model
- Physiology models (human, rabbit, and monkey)



The ocular model of the Additional Dosage Routes Module provides dosing as:

- Eye drop (topical solution or suspension)
- Intravitreal or subconjunctival implants
- IVT (intravitreal injection)

Some of the processes which can be modeled include:

- Nonlinear metabolism or transport in any eye tissue
- Convective flow incorporated into the ocular disposition model
- Two-site melanin binding options
- Predefined physiology models (human, rabbit, and monkey)

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Pulmonary (Intranasal/Respiratory) Model (Pulmonary Compartmental Absorption & Transit (PCAT™) Model

- Nonlinear metabolism or transport in any lung tissue!
- Age-dependent scaling of the pulmonary physiology!
- Physiology models (human, rat, mouse, and dog)

The pulmonary model provides dosing via the intranasal or respiratory route as an:

- Immediate release solution
- Immediate release powder

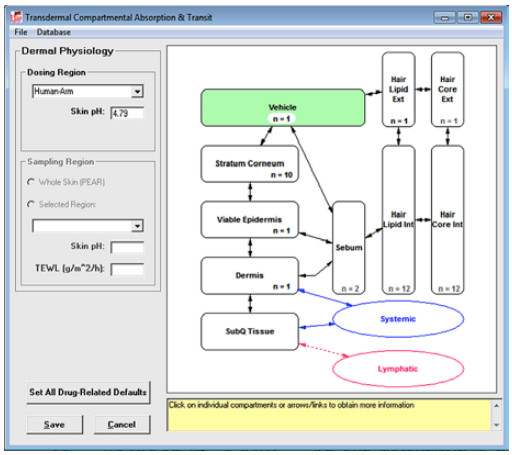
The pulmonary model includes the advanced ICRP 66 deposition model (Smith et al., 1999, LUDEP) for calculating deposition fractions in each compartment of both API and carrier particles. Additionally, you may account for the following processes in your simulations:

- Mucociliary transit
- Nonlinear metabolism or transport in any lung tissue
- Lymphatic transport & systemic absorption
- Age-dependent scaling of the human physiology

Dermal/Subcutaneous Model

The Transdermal Compartmental Absorption & Transit (TCAT™) model represents the skin as a collection of the following compartments: stratum corneum, viable epidermis, dermis, subcutaneous tissue, sebum, hair lipid, and hair core. The subcutaneous tissue is also considered. The diagram is shown in the figure below.

Updates to the dermal absorption (TCAT™) model through Cosmetics Europe project



The model can simulate a variety of transdermal & subcutaneous dosage forms, specified at different places on the body, including:

- liquid formulations (solutions, lotions, suspensions)
- semi-solid formations (gels, creams, lotions, pastes)
- subcutaneous injections (bolus or controlled release)

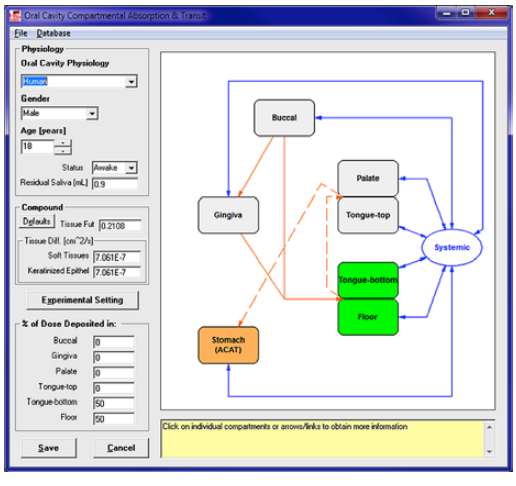
Some of the processes modeled include:

- vehicle evaporation
- absorption from the vehicle into the various tissue regions
- nonlinear metabolism in any tissue region
- systemic circulation and lymphatic absorption

Measured *in vivo* data for any dermal tissue can be used to compare with simulation results. All standard GastroPlus features, including the Population Simulator and Parameter Sensitivity Analysis, can be used with the dermal model.

Oral Cavity Delivery Model

The Oral Cavity Compartmental Absorption & Transit (OCCAT™) model represents the oral cavity (mouth) as a collection of the following compartments: buccal, gingival, palate, top of the tongue, bottom of the tongue, and mouth floor. The diagram is shown in the figure at right.



The model can simulate a variety of dosage forms including:

- sublingual solutions & tablets
- lingual sprays & supralingual tablets
- controlled release buccal patches

Some of the processes modeled include:

- dissolution & precipitation in the saliva
- diffusion through the oral mucosa

- uptake into systemic circulation
- swallowing of unabsorbed drug

Measured *in vivo* data for any oral cavity tissue can be used to compare with simulation results. All standard GastroPlus features, including the Population Simulator and Parameter Sensitivity Analysis, can be used with the oral cavity model.

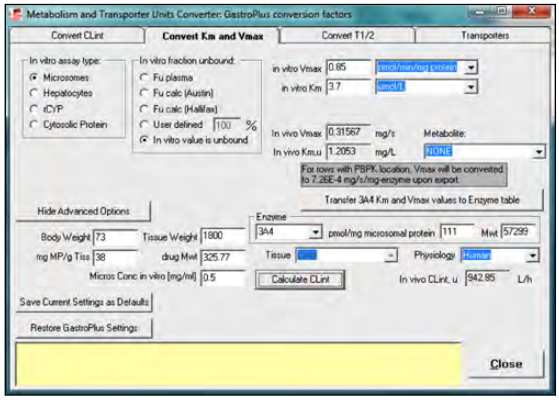
Metabolism and Transporter Module

When linked with the upgraded ADMET Predictor Module, predict CYP metabolism pathways & kinetics, and have the Enzyme Table automatically populated with the correct locations and units!

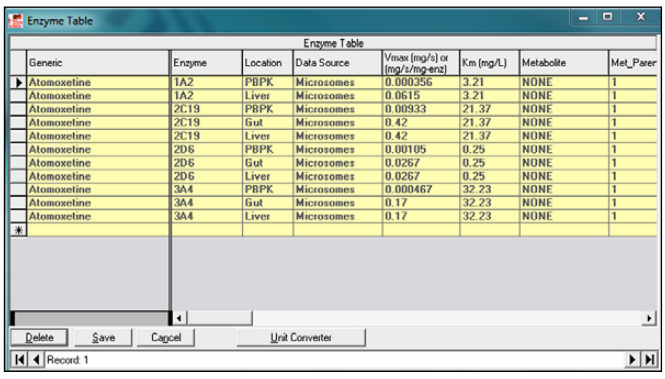
- Enzyme and transporter expression levels across species – including UGTs and SULTs!
- Metabolite tracking options!

The Metabolism and Transporter Module is an optional module that extends the capabilities of GastroPlus to include saturable metabolism and carrier-mediated transport into any compartment (gut, liver, and/or any PBPK tissue), along with metabolite tracking. This module calculates Michaelis-Menten rates for gut and liver (or any PBPK tissue) metabolism and for carrier-mediated transport (influx or efflux) based on input values for Vmax and Km. You can provide Vmax and Km values for each enzyme/transporter independently, or you can lump them into a single effective Vmax and Km, depending on your data. The distribution factors on the Physiology tab are automatically loaded for recognized gut enzymes and transporters, and provide the relative amounts of enzymes or transporters in the various ACAT™ gut model compartments. The Vmax and Km scale factors on the Pharmacokinetics tab are provided to allow fitting nonlinear kinetic models to your data.

The Metabolism and Transporter Module includes a Units Converter for easy transformation of a variety of your *in vitro* metabolism or transporter kinetic parameters into parameters and units that can be utilized by the GastroPlus model.



The Units Converter window provides a convenient way of converting *in vitro* measurements to *in vivo* inputs for the GastroPlus model.



Define multiple metabolic / transport pathways, with enzymes and transporters placed into the tissues or organs of your choice! Also, link formation of different metabolics in a single simulation!

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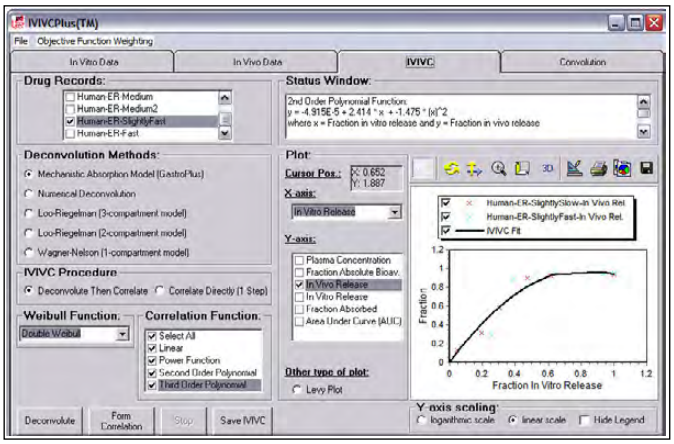
IVIVCPlus™ Module

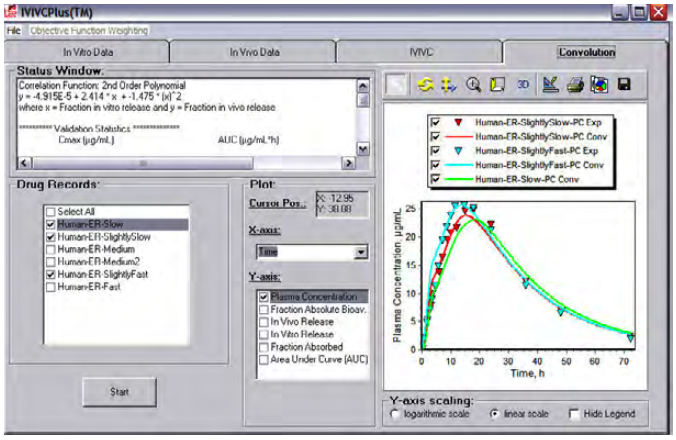
IVIVCPlus is an optional add-on module that provides a convenient way to develop a correlation between either *in vitro* release and *in vivo* release or *in vitro* release and absolute bioavailability. The formed correlation can then be used to predict PK profiles for formulations with different *in vitro* release rates.



GastroPlus was the first software program to offer "mechanistic deconvolutions", which deconvolute, or fit, the *in vivo* dissolution vs. time along the gut lumen. An advantage to using the mechanistic deconvolution method is that it can be linked to a PBPK model. We are pleased to validate the mechanistic deconvolution method through a 5-year **Research Collaboration Agreement with the U.S. FDA**.

IVIVCPlus offers five methods for deconvolution:

1) Mechanistic Absorption Model (GastroPlus)
2) Numerical Deconvolution
3) Loo-Riegelman (2-compartment model)
4) Loo-Riegelman (3-compartment model)
5) Wagner-Nelson (1-compartment model)



The Mechanistic Absorption Model (GastroPlus) deconvolution method directly deconvolutes the *in vivo* release rate. The other four methods are traditional deconvolution methods that calculate the rate of appearance of compound into the systemic circulation. For formulation scientists, the correlation between *in vitro* release and *in vivo* release is much more intuitive and valuable.

Depending on the deconvolution method selected, a correlation can be made between *in vitro* release and *in vivo* release or *in vitro* release and absolute bioavailability. Currently, linear, power, and polynomial (second or third order) functions may be selected for the functional form of the correlation.

Run Convolutions: The correlation function can be used to calculate an *in vivo* release-time profile or absolute bioavailability-time profile for a new formulation of the compound exhibiting a different *in vitro* release-time profile. A plasma concentration-time profile for the new formulation can be constructed with the calculated *in vivo* release-time or absolute bioavailability-time profile.

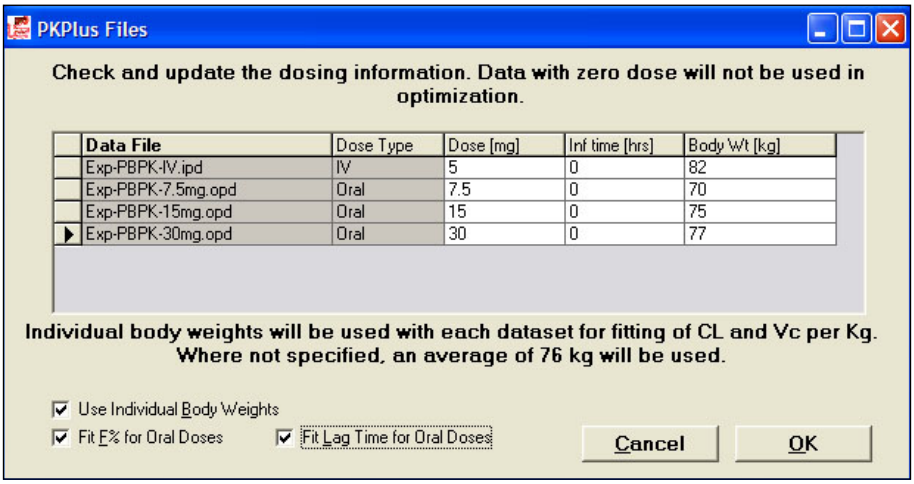
Evaluate Validation Statistics: After running a convolution, IVIVCPlus outputs the observed values, predicted values, prediction errors, and mean absolute percent prediction error for both Cmax and AUC. These statistics can be used to evaluate the internal or external predictability of the correlation as described in the FDA's "Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations".

New article from FDA scientists compares the Mechanistic Absorption deconvolution in GastroPlus vs. traditional methods – conclusion is that GastroPlus provides "greater predictive accuracy" - Mirza et al., Pharm. Res. 2012

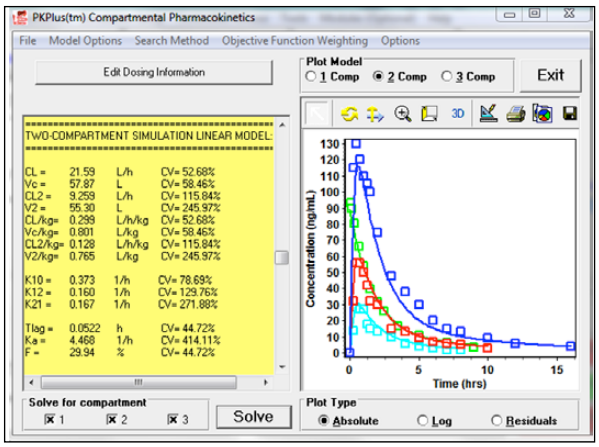
PKPlus™ Module

PKPlus extends GastroPlus to rapidly estimate pharmacokinetic (PK) parameters for non-compartmental analysis (NCA), along with 1-, 2-, & 3-compartment models from IV and oral plasma concentration-time (Cp-time) data, without the need to run full simulations. The fitted parameters include PK parameters, first order absorption rate, bioavailability and absorption lag time (if both IV and oral data are included in fitting). Required inputs are Cp-time profiles, dose, body weight and infusion time (if applicable). Compartmental PK can be fitted to single IV or oral data as well as across multiple Cp-time profiles - IV, oral, or combination of IV and oral as well as different dose levels. Linear or saturable clearance models can be selected easily.

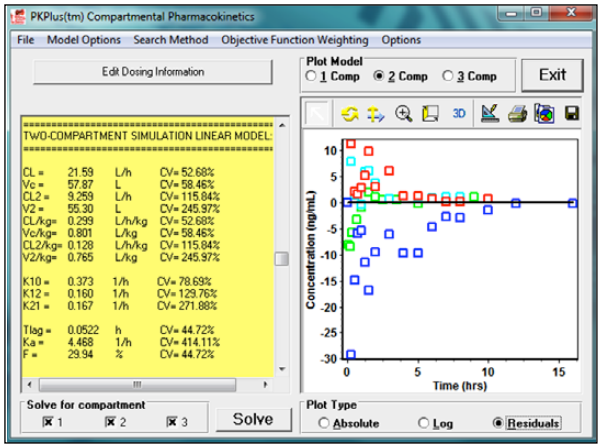
Full statistics, including Akaike Information Criterion and R^2, are provided for all models. Residual information is also captured and can be plotted. Once finished in PKPlus, the parameter values of the selected model can be easily transferred back to the main GastroPlus model, and all model results can be saved into report-quality outputs.



Plotting of absolute, log, and residuals for each model is selected with a mouse click, allowing rapid comparison of models.



2-compartment model for midazolam fitted across IV and three oral doses



Residuals plot for 2-compartment model for midazolam fitted across IV and three oral doses

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PDPlus™ Module

Automated model selection – fit across all direct and indirect models, along with phase-nonspecific cell killing options, with a single mouse click!

PDPlus allows you to fit standard pharmacodynamic (PD) models to observed data and use the fitted models to predict PD effect changes due to changes in dose, dosage form, and dosing regimens. The PDPlus module adds the Pharmacodynamics Table, which contains the PD model, the site of PD action, and the parameters that determine the kinetics of the action. Multiple PD models (therapeutic and adverse) can be accommodated for each drug record.

- PK-PD model additions to PDPlus™ Module
- Easily fit PD models across multiple data sets (e.g, doses)

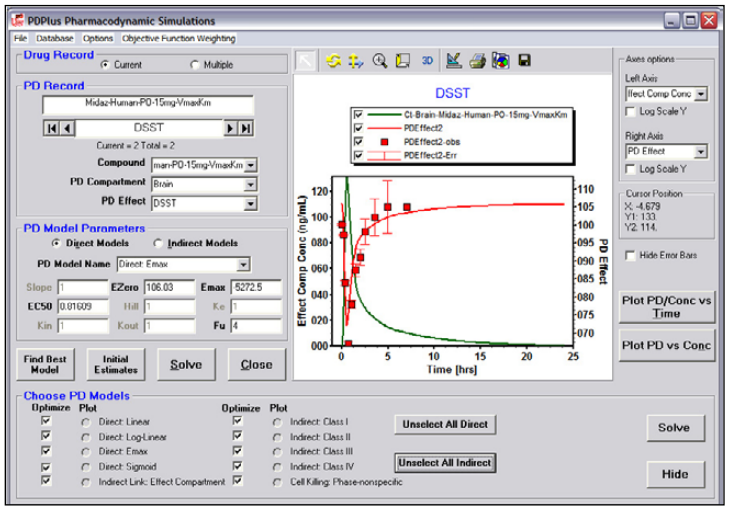
With PDPlus, fitting pharmacodynamic models to observed effect data is quick and easy. You may fit any of the standard PD models:

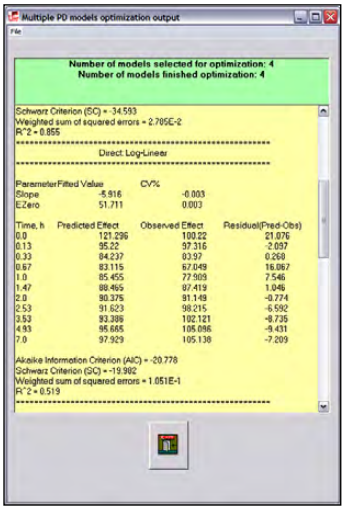
Direct Link: Linear, Log Linear, Emax and Sigmoid Emax

Indirect Link: Class 1, Class 2, Class 3, Class 4

Other: Phase-nonspecific cell killing (for tumor PBPK/PD modeling)

Convenient plotting of both plasma concentration-time and effect vs. time or concentration is provided with absolute and log plots available for each. Plus, all model results can be saved into report-quality outputs.





The effect can be linked directly to drug concentration in a specific tissue to easily perform PBPK/PD modeling.

Optimization Module

The Optimization Module for GastroPlus extends and enhances the program's basic capabilities in several important ways:

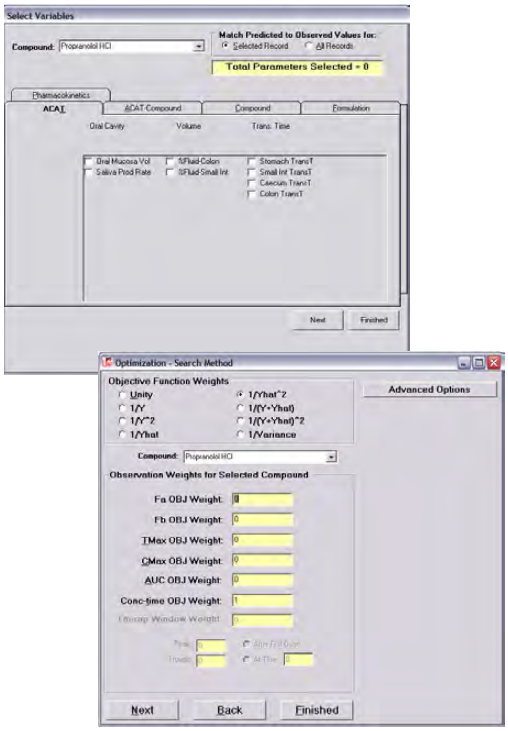
- To automatically fit model parameters to data
- To optimize study designs (e.g., dosing regimens) and dose

Fitting models to data

One of the most important uses of GastroPlus is to fit absorption, pharmacokinetic, and pharmacodynamic models to observations. In doing so, researchers gain tremendous insight into how their compound is behaving *in vivo*. When a single set of model parameters can be found that properly describes the observed plasma concentration-time for all dose levels, a useful model has been obtained. In general, if the model parameters must be changed for each dose level, then something is not being accounted for correctly. The Optimization Module performs the multidimensional search needed to fit model parameters to one or more data sets automatically.

Model fitting can include (but is not limited to):

- PBPK model parameters to plasma and/or tissue concentration vs. time data
- Peff and absorption scale factors to determine regional dependencies
- A wide variety of physiological parameters (when necessary)
- Parameters to match profiles of parent drugs or any of their metabolites



Model parameters can be fitted to data for a single record, or across multiple records simultaneously. The program will run one simulation for each record each time it changes the value(s) of one or more model parameters. Typically, hundreds of iterations will be performed, each with N simulations, where N is the number of records whose observations are being used to compare predicted and observed values. Objective function weighting is user-defined, and includes the most common weighting schemes.

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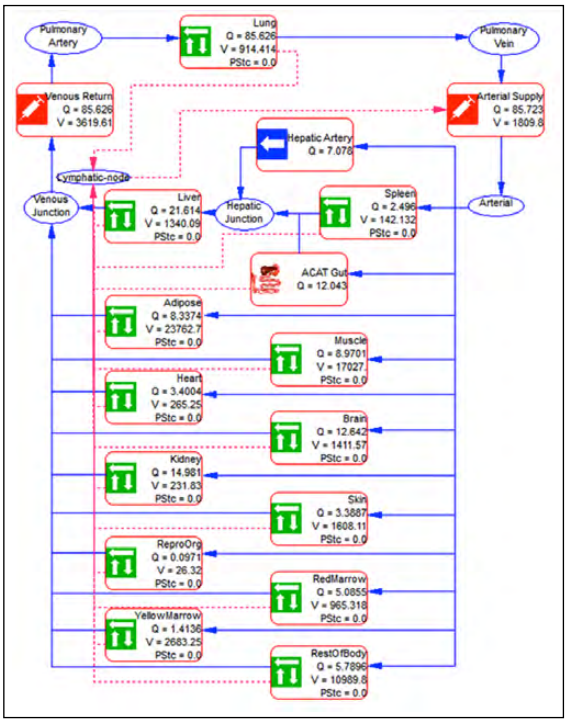
Biologics Module

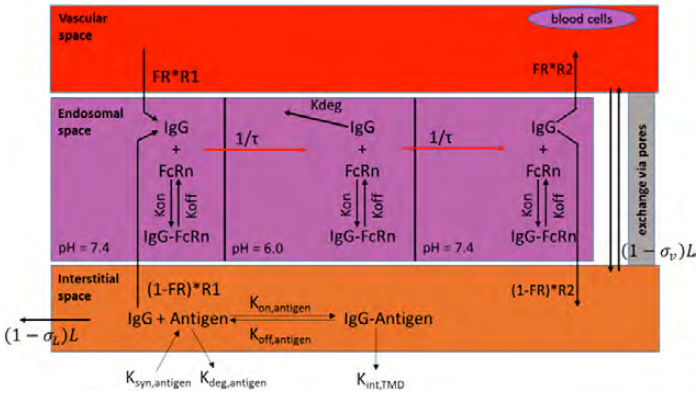


Each organ in the PBPK model is divided into three major compartments representing the vascular, endosomal, and interstitial spaces, as shown in the image at right.

PBPK models for antibody-drug conjugates (ADCs)

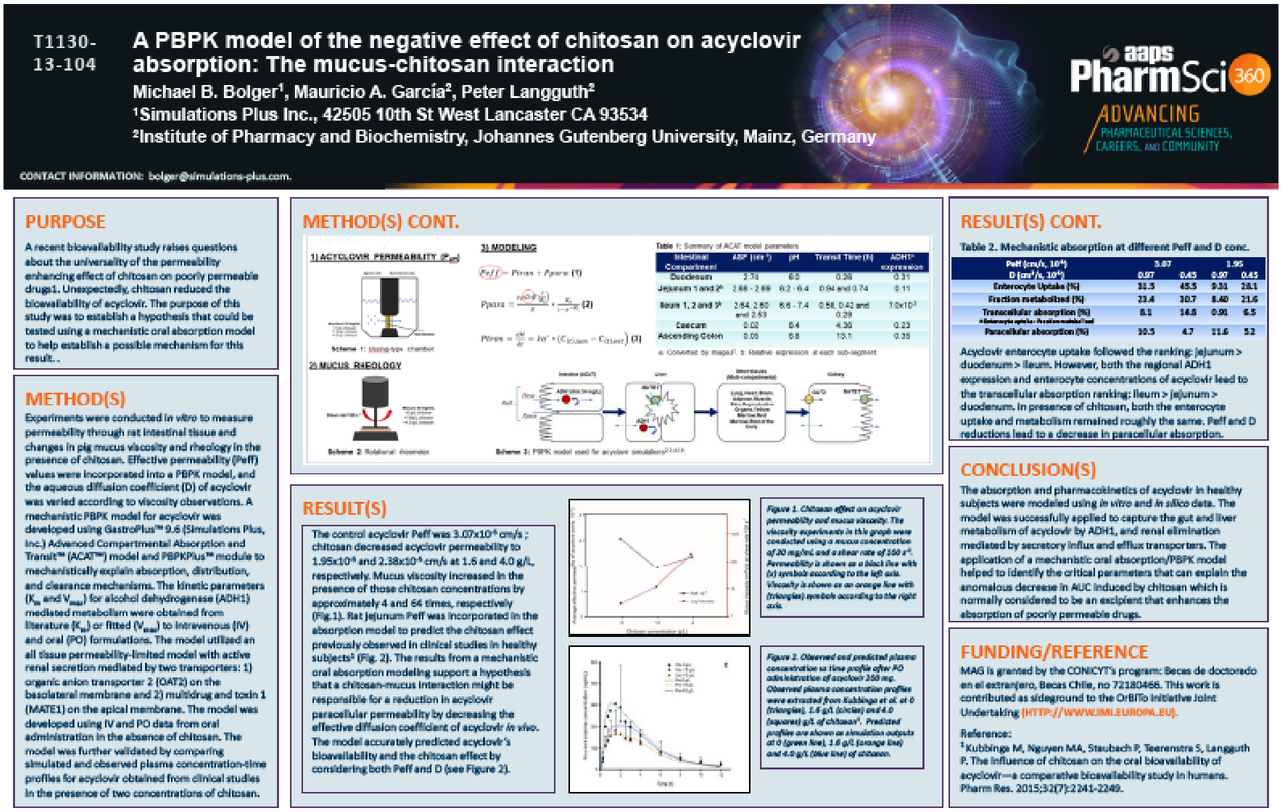
Starting in GastroPlus 9.0, we are pleased to offer PBPK models for large molecules (biologics). The Biologics Module simulates the absorption, distribution, and clearance of biological drugs. In the current implementation, both monoclonal antibodies (mAb) and antibody-drug conjugates (ADCs) administered as an intravenous bolus dose, intravenous infusion, or subcutaneous (SQ) injection can be modeled. As with other GastroPlus modules, there is no equation or code writing required. A schematic diagram of how the different organs are connected to one another is shown at left.

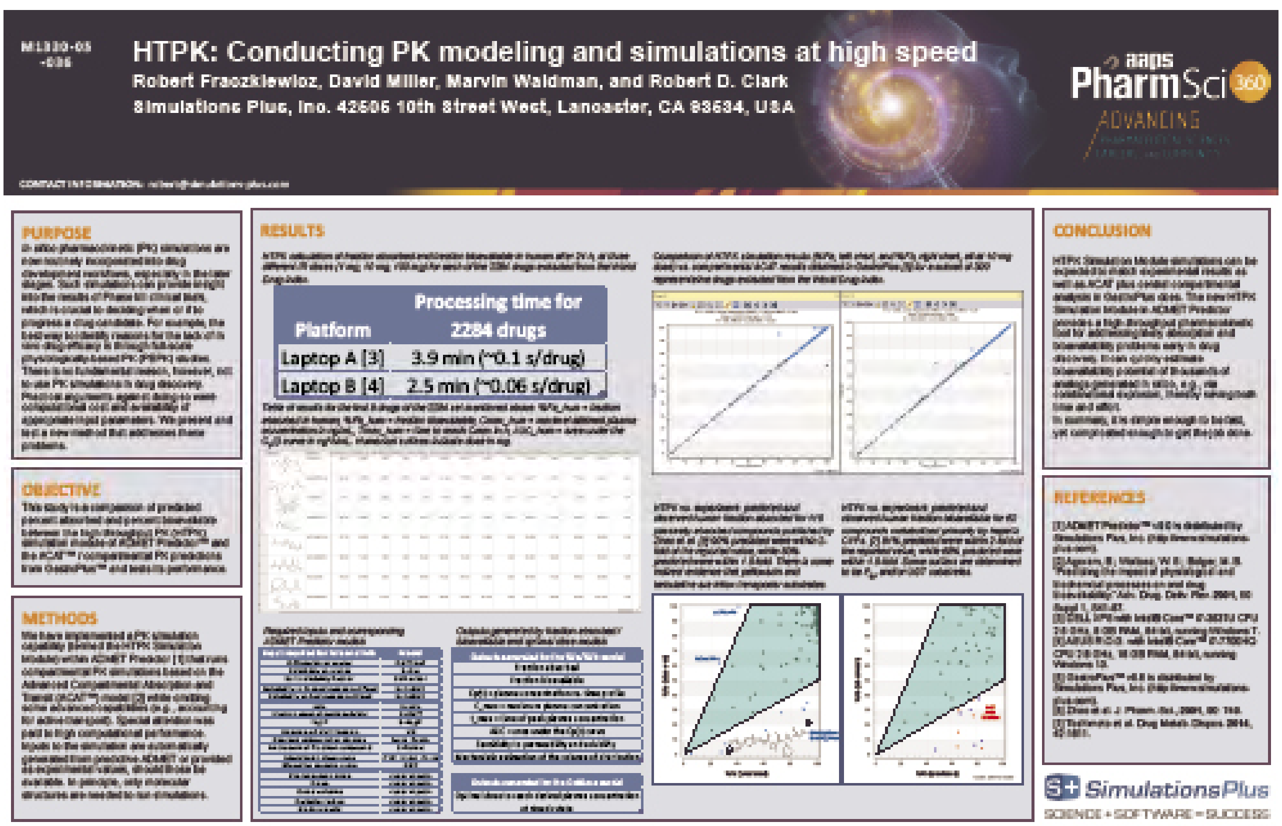
All major organs are connected in an anatomical fashion with plasma flow represented by blue solid arrows and lymph flow by red dashed arrows. The lymph node collects the lymphatic drainage from organs and lymph fluid is returned to the systemic circulation. Each organ in the PBPK model is divided into three major compartments representing the vascular, endosomal, and interstitial spaces, as shown below.

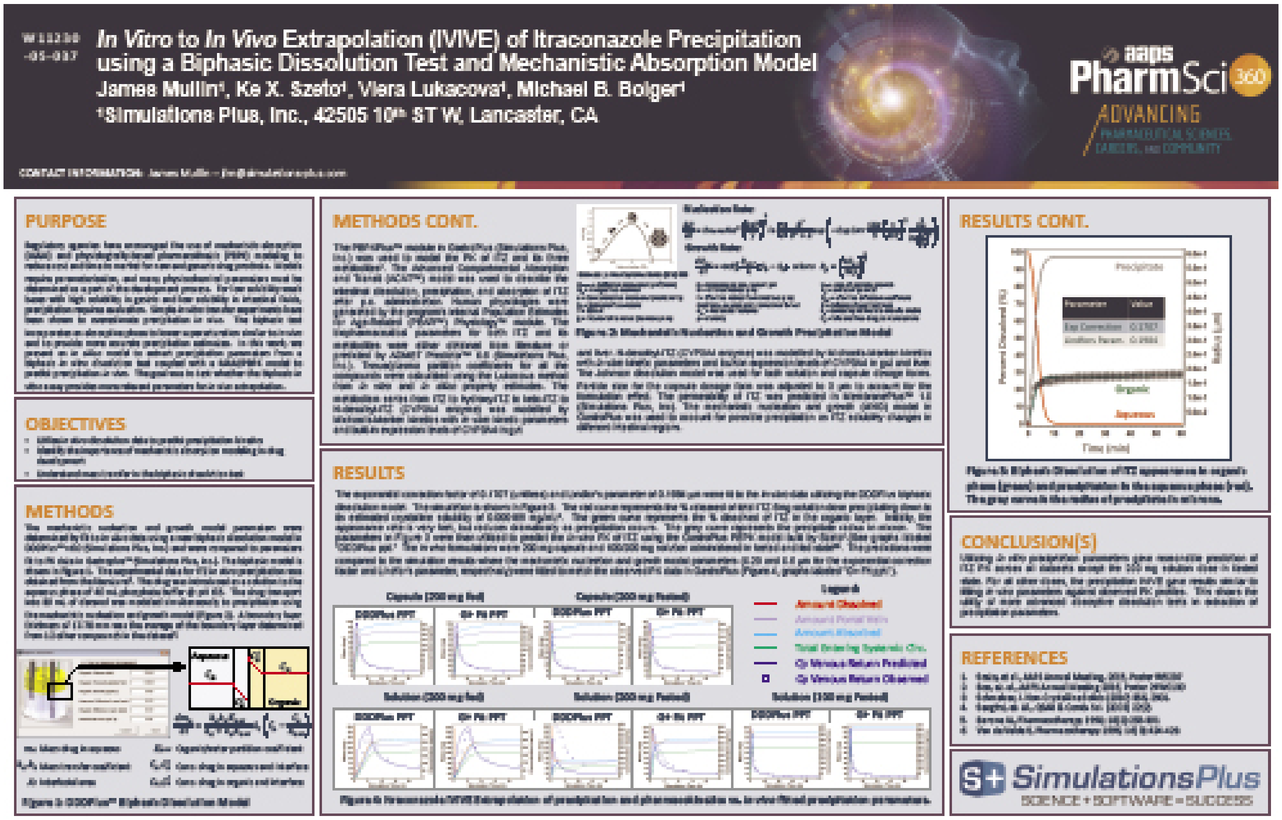


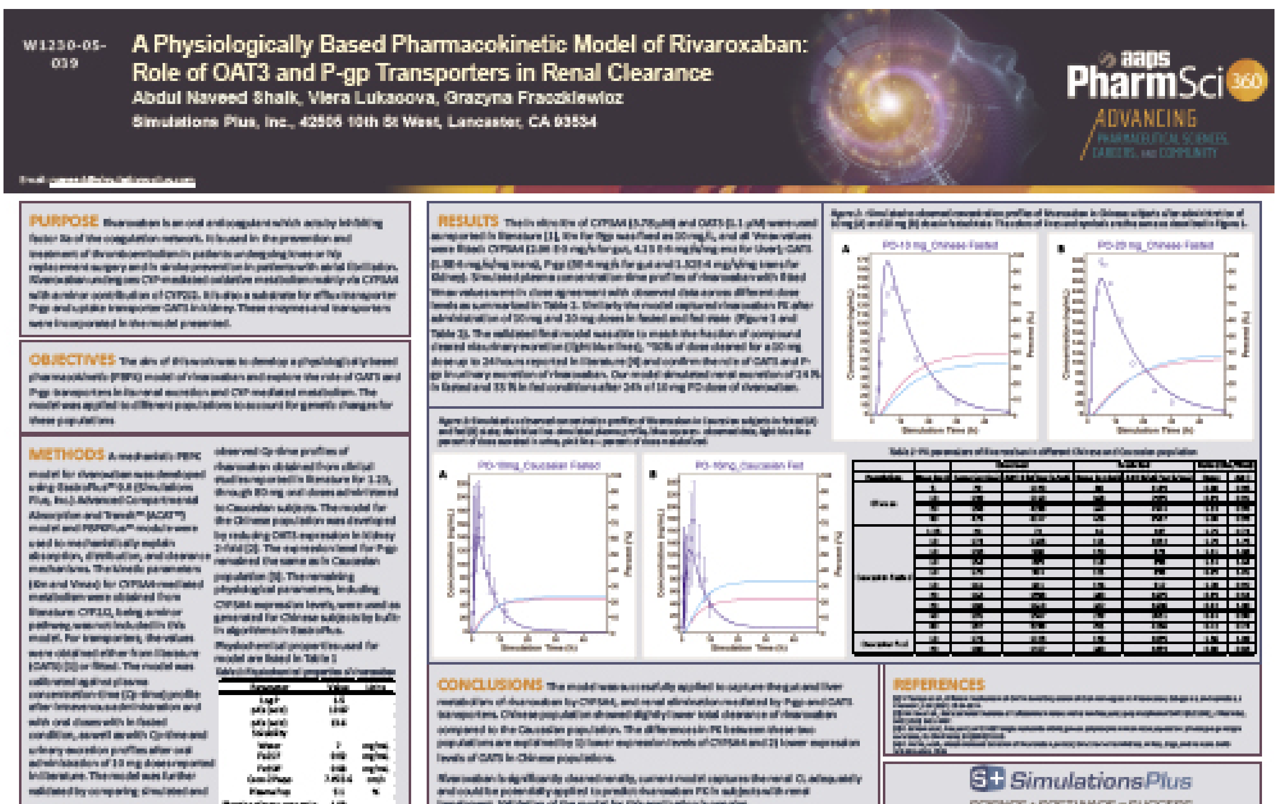
Some of the key processes accounted for in the GastroPlus models include:

- Convective transport and fluid phase endocytosis describing uptake of antibody into the tissue
- mAb-FcRn (neonatal FC receptor) binding & recycling
- Target mediated elimination in the interstitial space to include the influence of specific antigen-mAb interactions on mAb disposition
- Within the endosomal space, the competition for binding to FcRn between endogenous IgG and the therapeutic mAb
- mAb administration by either intravenous (IV) or subcutaneous (SQ) injection
- Complete default physiology parameters for humans – flexibility to create custom species models
- With ADCs, distribution and elimination processes of multiple ADC species with different DAR (drug-to-antibody ratio):
  - o Distribute to peripheral compartments
  - o Cleared by nonspecific clearance
  - o Bind to target receptor, internalize, and be cleared in the cell lysosome









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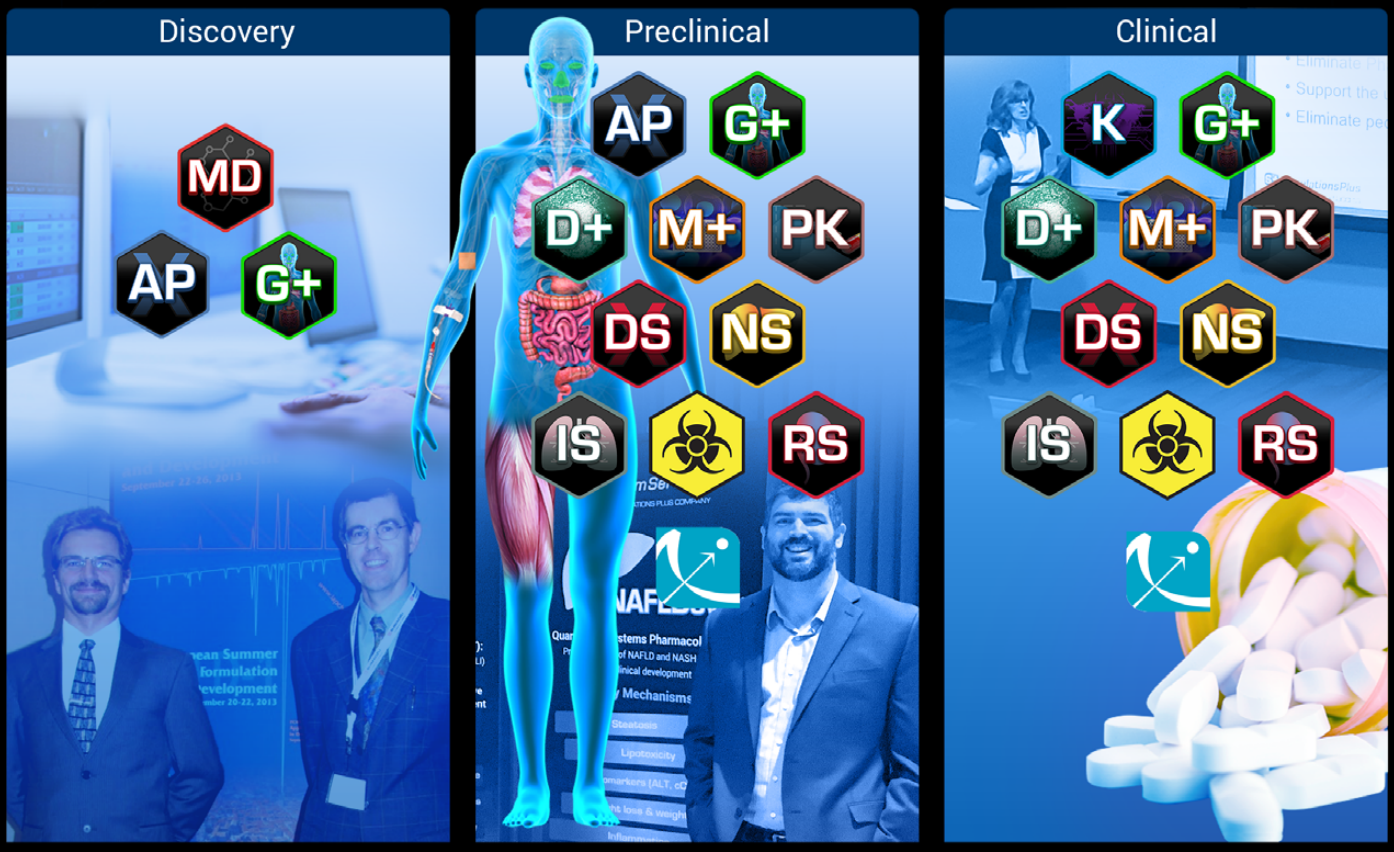

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