



SCIENCE + SOFTWARE = SUCCESS

GastroPlus® v9.7

May 2019

Dear GastroPlus® User,

Thank you for your interest in GastroPlus. Our Simulations Plus development team continues to work hard to make GastroPlus the most advanced and reliable simulation of drug absorption, pharmacokinetics, and pharmacodynamics in the world today.

1. Updates in version 9.7

- ACAT™ Model:
 - Allow two solubility inputs for different drug forms (crystalline, amorphous)
 - Fed state conditions based on meal type
- Additional Dosage Route Module:
 - Dermal: Compound evaporation with topical administration
 - Intramuscular: Effect of immune response with intramuscular injection
- ADMET Predictor® Module:
 - Predictions of compound interaction (substrate and/or inhibitor) with additional transporters (OCT2, BSEP, BCRP)
- DDI Module:
 - New validated compound model files (Alfentanil, Efavirenz, Voriconazole,) in the DDI standards database
- Metabolism and Transporter Module:
 - New enzyme/transporter distribution information
 - Provide expression levels of enzymes for extensive, intermediate, and poor metabolizers based on specific genotypes
- PBPKPlus™ Module:
 - Mechanistic pregnancy PBPK model
 - Lysosomal trapping in calculation of tissue/plasma partition coefficients
 - Allow different tissue model types (perfusion- or permeability-limited) for different compounds in simulation
- PDPlus™ Module:
 - New precursor-dependent indirect models
- General Features:
 - Flexibility in solubility vs. pH model fitting
 - Updates in Peff converter
 - Bug fixes

2. Updates in version 9.6

- ACAT™ Model:
 - New human physiologies with dynamic intestinal fluid in fasted state
 - Revisited colon enterocyte volume calculations for all species
- Additional Dosage Route Module:
 - Ocular: Mechanistic enhancements in model structure and updated default estimates for



SCIENCE + SOFTWARE = SUCCESS

- permeabilities and systemic absorption rate constants
- Pulmonary: New particle deposition model (Finlay)
- Dermal: Option for quick setup of *in vitro* skin permeability assays
- Intramuscular and Subcutaneous: Added dissolution/precipitation processes for small molecules
- ADMET Predictor® Module:
 - Predictions of rat-specific properties (Fup, blood/plasma concentration ratio, hepatic CLint)
 - Predictions of clearance mechanism classification and Extended Clearance Classification System (ECCS)
- DDI Module:
 - New validated compound model files (Diltiazem, Raltegravir, Bupropion, Atazanavir, Dolutegravir) in the DDI standards database
- DILIsym®:
 - Run population simulations for groups of subjects matching body weights from DILIsym SimPops™/SimCohort™
 - Save simulation results in a DILIsym input file
- IVIVCPlus™ Module:
 - Now linked with non-oral controlled release formulations
 - New time scale/shift correlation function
 - Option to use triple-Weibull function for mechanistic deconvolution
 - Option to use interpolated *in vitro* profile for IVIVC generation
 - More control over optimization criteria with mechanistic deconvolution
- Metabolism and Transporter Module:
 - New built-in enzyme and transporter distribution information in human and several animal species
- PBPKPlus™ Module:
 - Revised all human PBPK physiologies with improved covariate algorithms
 - New built-in models for disease conditions (obesity and renal impairment)
 - Option to specify clearance directly in blood compartments
- PDPlus™ Module:
 - New bacteria killing PD models
- General Features:
 - Improved simulation performance (faster simulations)
 - Updates in the Population Simulator:
 - Improved covariates handling
 - Modified algorithms for creating virtual populations to give the user more control over subject parameters (age, weight and BMI range)
 - New options for saving simulation results in Batch, PSA, and Population Simulator:
 - Option to save selected simulated profiles (in addition to plasma concentrations) in every analysis
 - Option to save the results in an easy-to-read Excel format
 - Bug fixes

3. Installation of GastroPlus on your computer/Network

GastroPlus is a modeling & simulation software program designed to run on Windows 7, 8, and 10



SCIENCE + SOFTWARE = SUCCESS

systems, or Mac computers through Parallels (or similar Windows virtualization). GastroPlus can be installed from the *.zip package retrieved from [our ShareFile online portal](#), either as a “standalone” installation on your computer or as a “network installation” on your local area network. Refer to the installation manual for detailed instructions on the installation process.

Before GastroPlus can be run from your installation, it has to be activated. The activation process is handled via email with our licensing department. Should you have any questions, please contact one of our customer support representatives at: licensing@simulations-plus.com or +1-661-723-7723.

4. GastroPlus tutorial

GastroPlus includes an extensive help file with a re-designed tutorial for new users. This tutorial can be used by prospective customers during the evaluation of GastroPlus, or by new/existing customers to assist with validating a computer system (i.e., running tutorials to confirm the same results are generated on your computer versus what is reported in the tutorial).

The tutorial document contains step-by-step instructions for running GastroPlus simulations. A few standard simulations and their use in drug development are described. Data for running these simulations are also provided wherever necessary, along with the nature and source of the data. The tutorial data files are present in the Tutorials folder after installing GastroPlus on your computer.

5. Customer support

As part of our Personal Consultation Program, Simulations Plus has assigned scientists to specifically serve you in your use of GastroPlus. Feel free to contact them for advice on techniques for using the program better, for suggestions, and bug reports.

We stand ready to help you. If you need assistance in getting started, or if you would like advice on techniques for using the program most effectively in your research, please feel free to contact us.

Telephone: +1-661-723-7723
Fax: +1-661-723-5524
E-mail: info@simulations-plus.com
Website: www.simulations-plus.com

We look forward to serving you and assisting in any way we can.

Best regards,

John DiBella
President, Lancaster Division
Simulations Plus, Inc. (NASDAQ : SLP)



SCIENCE + SOFTWARE = SUCCESS

The Development Team:

Scientists/Programmers:

Haiying Zhou, Ph.D.
Jessica Spires, Ph.D.
Jim Mullin, M.S.
Ke Xu, Ph.D.
Azar Shahraz, Ph.D.
Maxime Le Merdy, Ph.D.
Manas Shah, Ph.D.
Robert Fraczekiewicz, Ph.D.
Michael B. Bolger, Ph.D., Chief Scientist
Viera Lukacova, Ph.D.

Graphic Art:

Victor Aguilar

Security, Installation, and Network Support:

Mark Pflieger
Kevin Cooper
Brandon Rodriguez

Compiled May 2019