SCIENCE + SOFTWARE = SUCCESS

GastroPlus® v9.8

October 2020

Dear GastroPlus® User,

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

1. Updates in version 9.8

- ACAT™ Model:
  - Conversion of glucuronide metabolite back to parent compound in the gut lumen
  - Mechanistic treatment of cyclodextrin formulations
- Additional Dosage Route Module:
  - NEW: Intraarticular administration
  - NEW: Inhalation of volatile compounds in the pulmonary (PCAT™) model
  - Pulmonary (PCAT™): Addition of lysosomal trapping mechanism
  - Ocular (OCAT™): Topical ointment administration; Protein binding in tissues
  - Dermal (TCAT™): Flexible dermal dosing through mixed multiple doses (*.mdd) file; Updated model for sebum permeability
  - Intramuscular and Subcutaneous: Extensions for Long Acting Injectable formulations
- ADMET Predictor® Module:
  - Machine learning predictions of compound interaction (substrate and/or inhibitor) with additional transporters (OATP1B3, OAT1, OAT3, OCT1, OCT2)
  - Machine learning predictions of Km values for number of transporters (OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2)
- DDI Module:
  - New or updated validated compound model files with documentation ready for regulatory submissions
- Population Simulator:
  - Automated execution of repeated trials
  - Intrasubject variability with crossover trials
  - Updated physiological CVs for many intestinal parameters
- PBPKPlus™ Module:
  - Extension of lung tissue to account for drug partitioning into the lung fluid for fit-for-purpose discovery modeling
- General Features:
  - Bug fixes

2. 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

3. Installation of GastroPlus on your computer/network

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

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

Best regards,

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