Oral drug absorption modeling in PK-Sim® Hands-on exercises Aid

April 16, 2021

This document is intended to help participants conducting the hands-on exercises included in Session 2: Oral drug absorption modeling in PK-Sim®.

The purpose of these exercises is to increase participants experience with oral drug absorption modeling in PK-Sim. The included information in this document can be used as inspiration or points of direction, it does not provide complete step-by-step instructions.

Session 2
- Oral drug absorption modeling PK-Sim®

- Welcome & OSP Intro *(20 min)*
- PK-Sim oral absorption model *(45 min)*

Break 10 min

- **Hands-on exercises**
  - Intro 1 *(5 min)*
  - Establish oral absorption model *(30 min - breakout rooms)*
  - Intro 2 *(5 min)*
  - Formulation performance in virtual populations *(30 min - breakout rooms)*

Break 10 min

- Virtual bioequivalence framework (FDA grant U01FD006549) *(45 min)*

Session 2 - Hands on
Part 1 – Establish oral absorption model

Task: Establish oral absorption model for “Drug” using data after oral solution administration as reference.

Systemic disposition already established.

Information of relevance for oral absorption model development

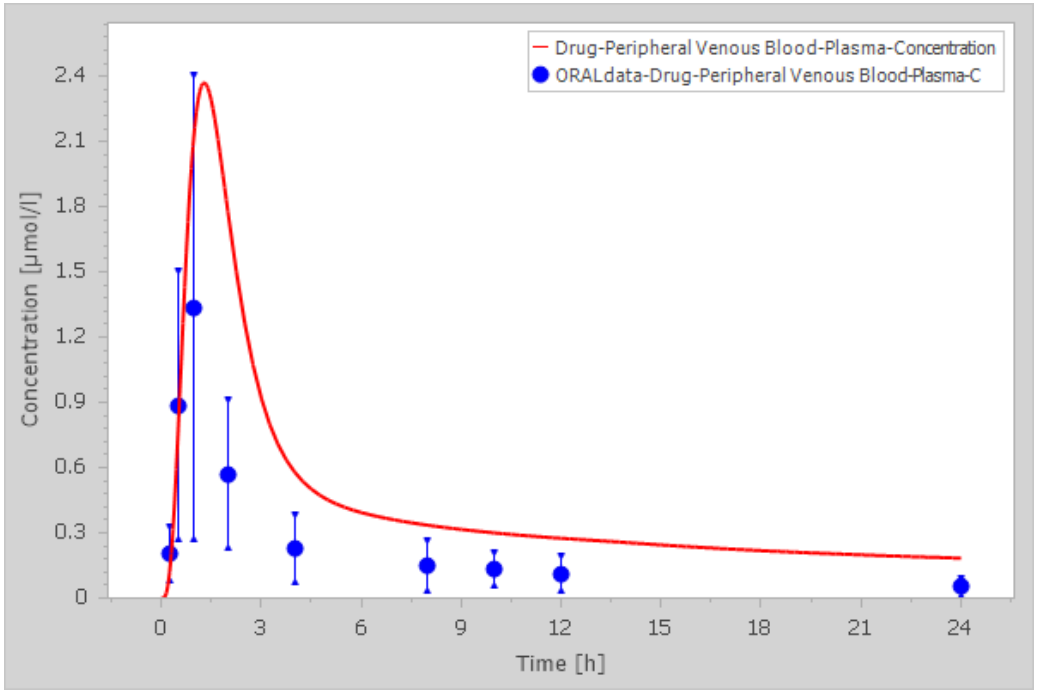
- Internal data (not shown) suggests
  - Incomplete absorption
  - Gut wall metabolism in small intestine
  - Negligible absorption in colon (colon ascendens - rectum)

If time allows: Investigate transporters and EHC. Reflect on potential impact on systemic disposition

Session 2 - Hands on
Part 1 – Establish oral absorption model

1: Set up simulation for oral administration

- Clone simulation “IV_100mg”, name “ORAL_100mg”
- Select Administration protocol “ORAL_100mg” and formulation “Solution”
- Remove “Ivdata” and add “ORALdata” as observations

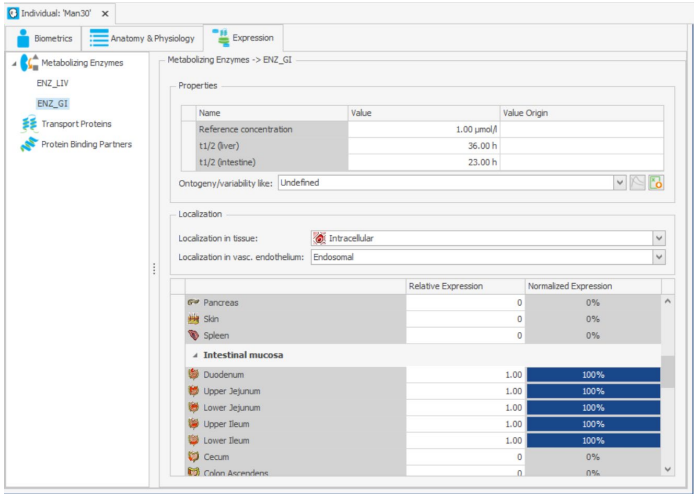


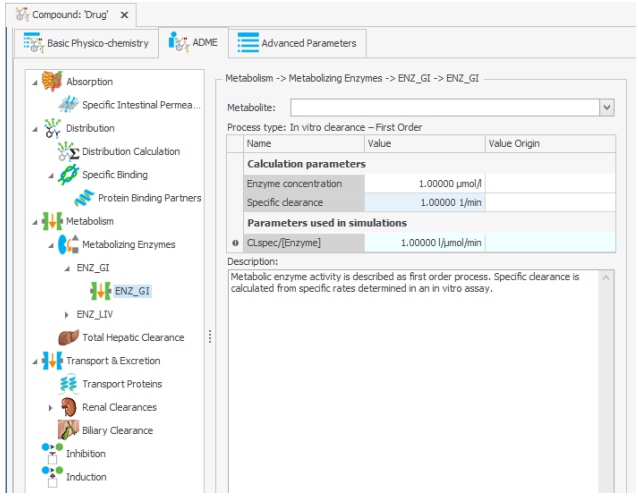
Session 2 - Hands on

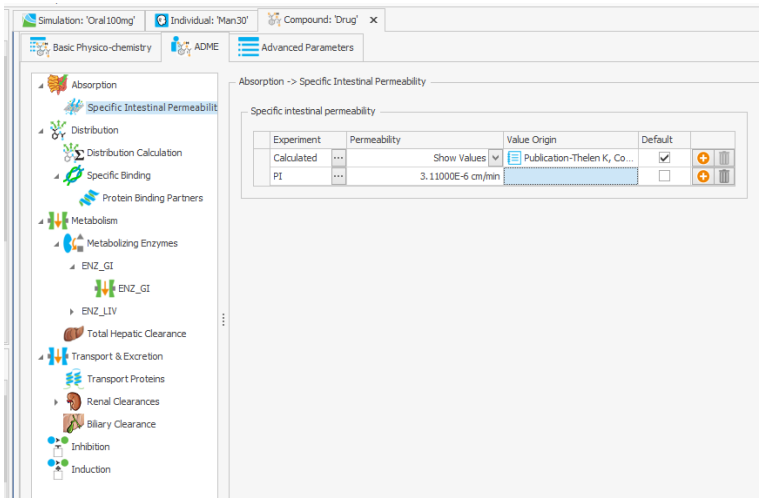
Part 1 – Establish oral absorption model

2a: Preparation prior improvement of Oral model performance

- For Individual “**Man30**”: Add ENZ_GI with relative expression = 1 in small intestine mucosa. Keep other input as default.
- For Compound “**Drug**”: Add “Metabolizing enzyme” for ENZ_GI, in vitro CL- first order, Enzyme concentration and Specific clearance1 µmol
  Create new “specific intestinal permeability value” (PI) set to calculated value (3.11E-6 cm/min)





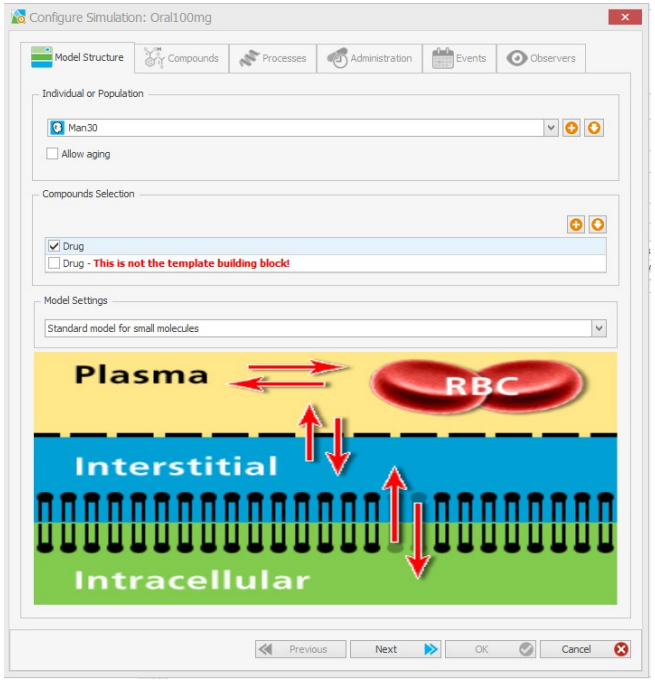


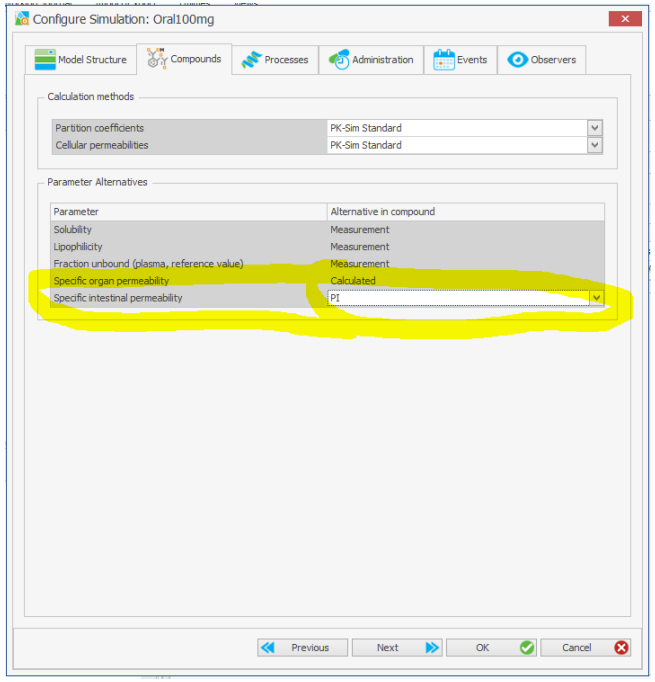
Session 2 - Hands on

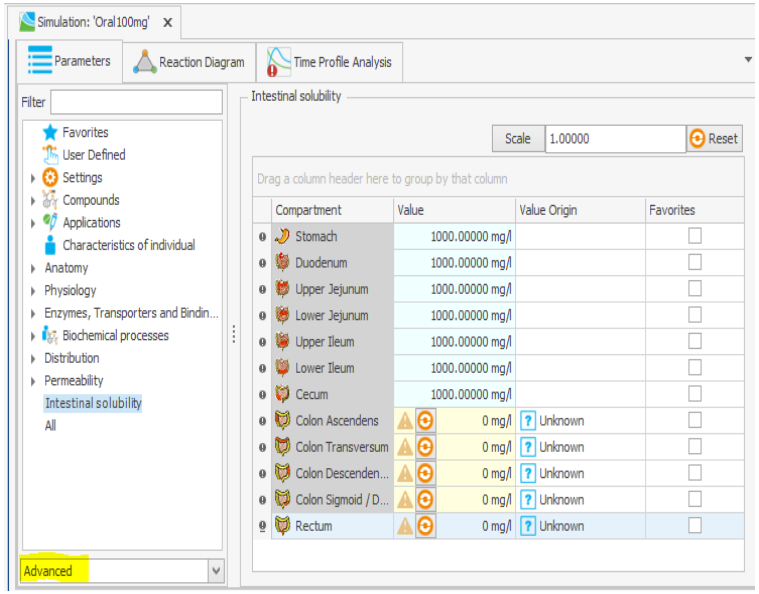
Part 1 – Establish oral absorption model

2b: Preparation prior improvement of Oral model performance

- For Simulation “**ORAL_100mg**”: Update “Man30” and “Drug”. Select the “Drug” in automatically opened configuration window
  Use new permeability value (PI) from drop-down.
  Exclude absorption from colon ascendens – rectum e.g. by setting intestinal solubility (visible in “Advanced” view-mode) to 0 in these compartments (can be achieved in other ways).





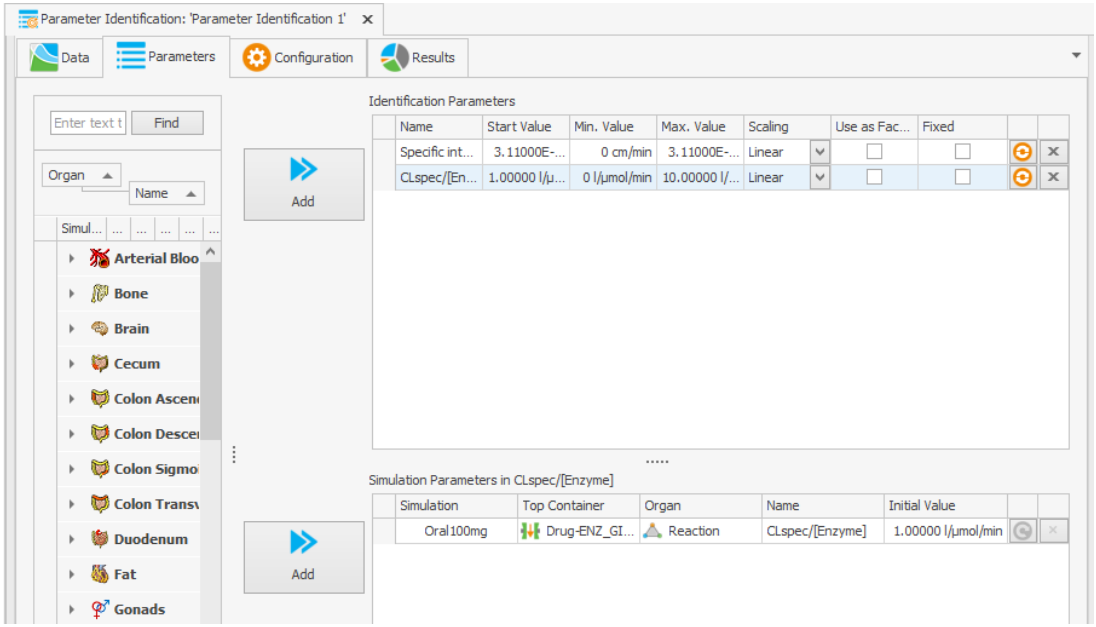


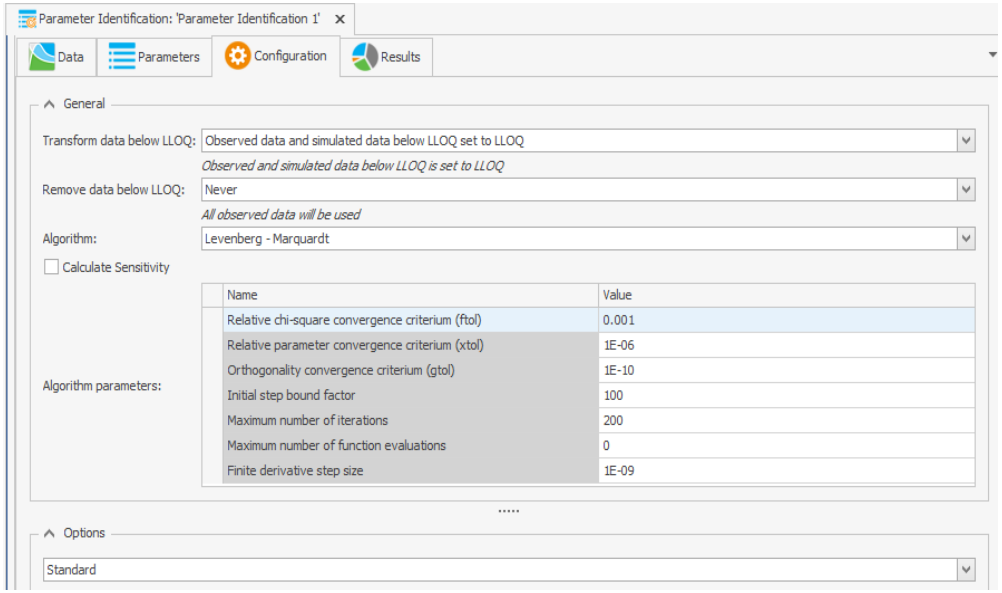
Session 2 - Hands on

Part 1 – Establish oral absorption model

3a: Perform Parameter Identification and update “Drug” building block

- Create a “Parameter Identification” and include “ORAL_100mg”
- Select “Specific intestinal permeability (transcellular)” and “CLspec/[Enzyme]” for ENZ_GI
- Set “Configurations”, or leave as is
- “Run”



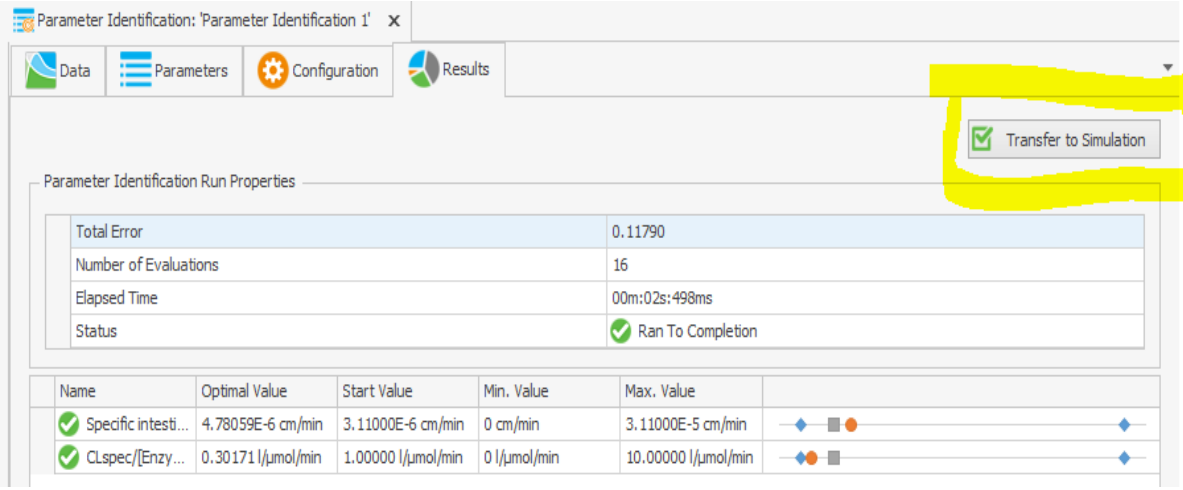


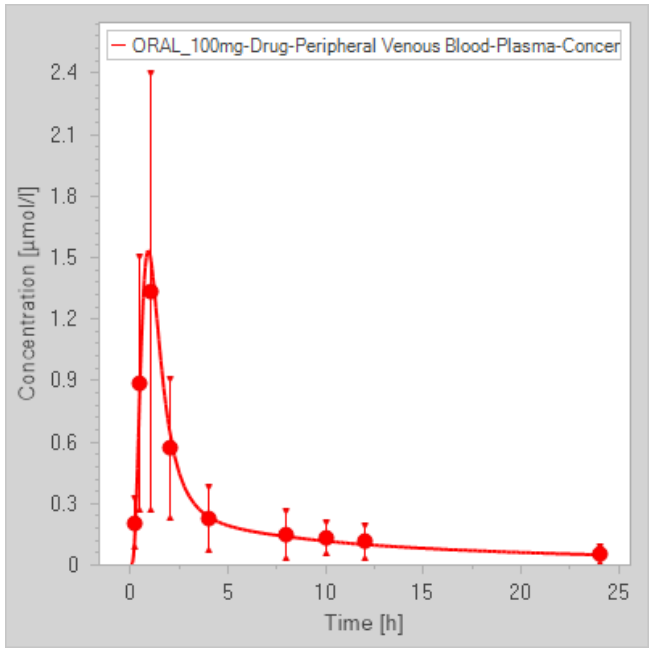
Session 2 - Hands on

Part 1 – Establish oral absorption model

3b: Perform Parameter Identification and update “Drug” building block

- “Transfer to Simulations” from “Results” if adequate parameter estimates have been achieved.
- Update “Drug” building block

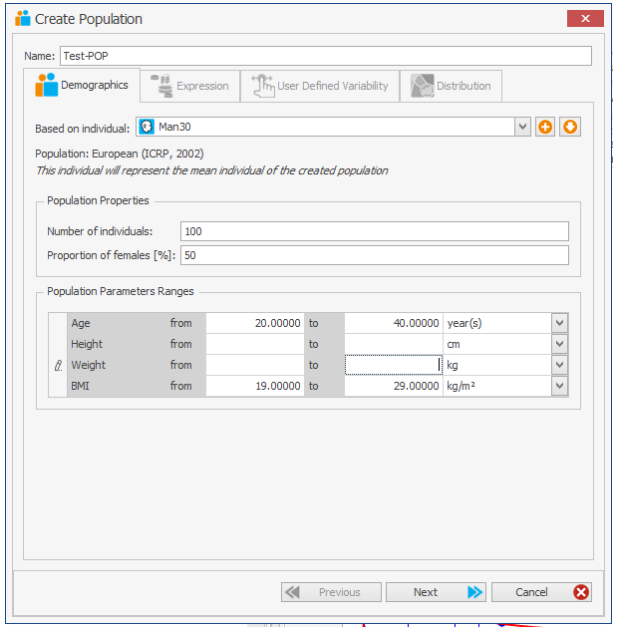


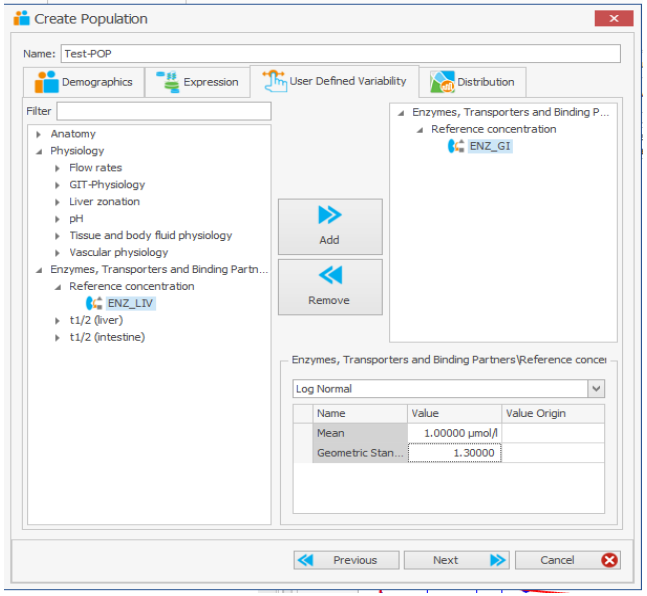


Session 2 - Hands on
Part 2 – Formulation performance in virtual populations

Task: Evaluate formulation performance in virtual population with established model.

- Create a representative trial population (Age, BWT, and HT)
  - Optional: Add variability in metabolism by adding variability on abundance (liver and/or intestine)

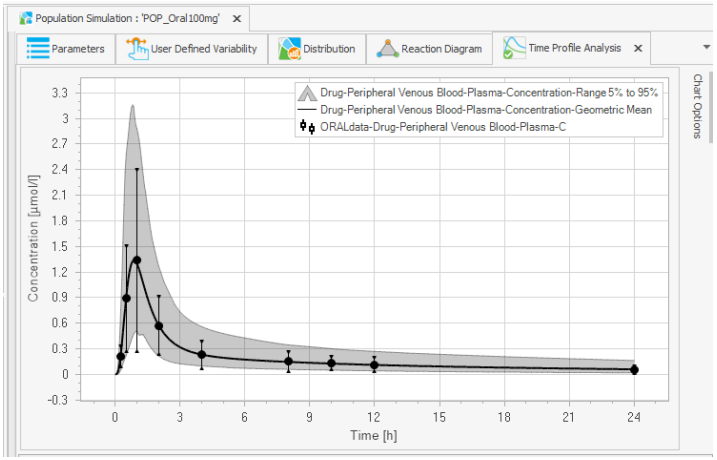




Session 2 - Hands on
Part 2 – Formulation performance in virtual populations

Task: Evaluate formulation performance in virtual population with established model.

- Perform virtual trial simulations for Reference and Test formulations (n=3).
  - Run simulations
  - Assess output visually.



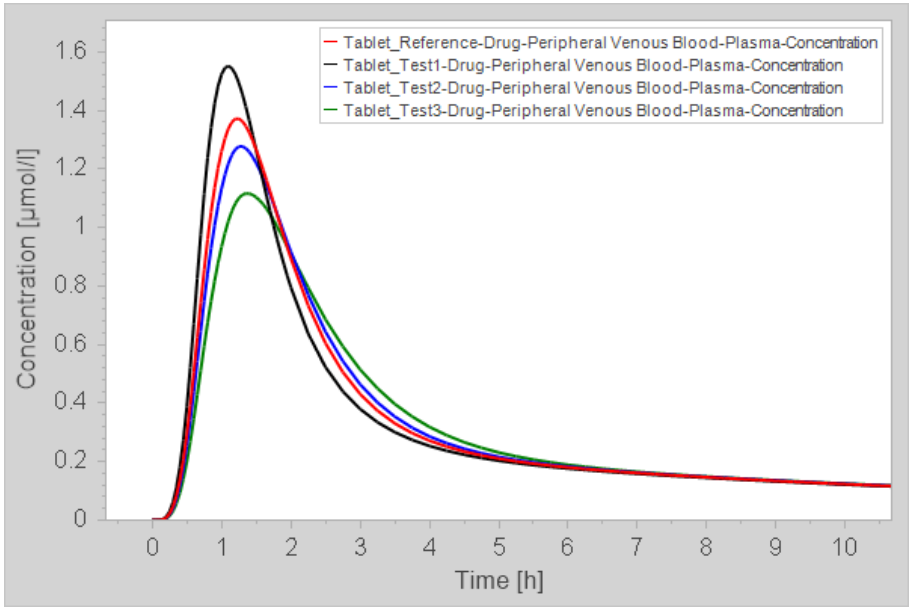
If time allows:

- Evaluate impact of population variability on AUC and Cmax.
  - After intra venous administration
  - After oral administration

Session 2 - Hands on
Part 2 – Formulation performance in virtual populations

1: Set up simulations for oral administration of the tablet formulations for typical individual

- Clone simulation “ORAL_100mg”, Name “Tablet_Reference”
- Select respective formulation, “Tablet_Reference”, “
- Remove “ORALdata” observations
- Clone simulation “Tablet_Reference” to create simulations “Tablet_Test1” , “Tablet_Test2” and “Tablet_Test3”.
- *Optional: Add output such as “fraction absorbed” or “fraction dissolved” for additional means of evaluation*



Session 2 - Hands on
Part 2 – Formulation performance in virtual populations

2: Create a generic virtual population and perform virtual population simulations

- Create virtual population based on ”Man30”, e.g., age 25-40 , 100% men, n=100.
- *Optional: Add additional variability under “User Defined Variability”*
- Clone tablet simulations, add suffix “_POP”, and replace ”Man30” with created virtual population
- Run simulations
- For visual evaluation in PK-Sim use “Compare Results” functionality