



# 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)

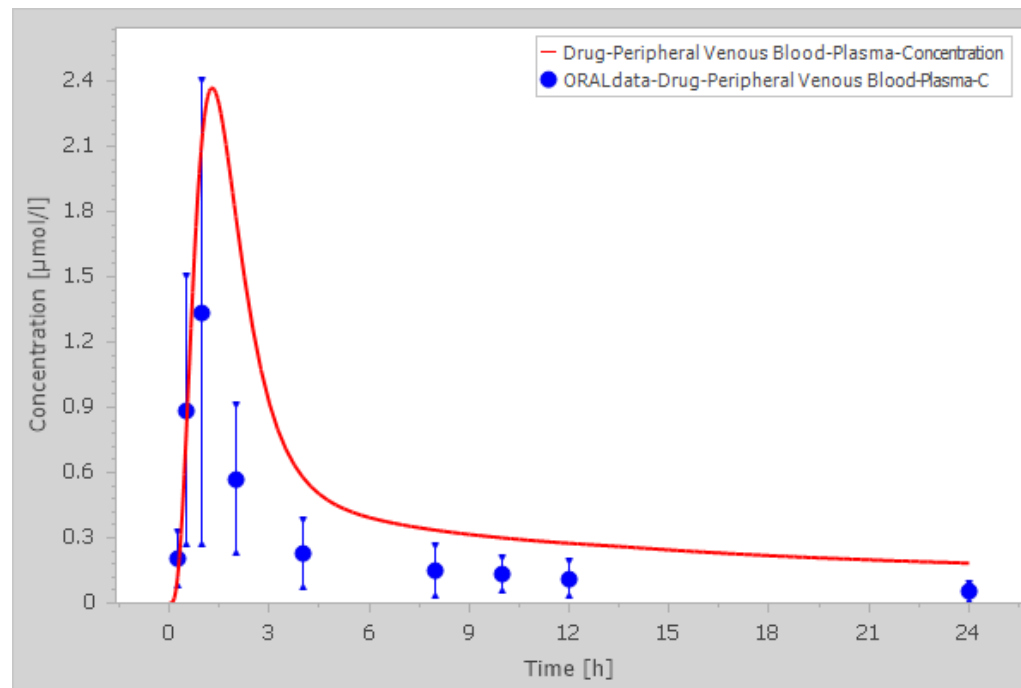
If time allows: Investigate transporters and EHC. Reflect on potential impact on systemic disposition

# 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 clearance  $1 \mu\text{mol}$   
Create new “specific intestinal permeability value” (PI) set to calculated value ( $3.11\text{E-}6 \text{ cm/min}$ )

Individual: 'Man30'

Metabolizing Enzymes -> ENZ\_GI

Name	Value	Value Origin
Reference concentration	1.00 $\mu\text{mol/l}$	
t1/2 (liver)	36.00 h	
t1/2 (intestine)	23.00 h	

Ontogeny/variability like: Undefined

Localization

Localization in tissue: Intracellular

Localization in vasc. endothelium: Endosomal

	Relative Expression	Normalized Expression
Pancreas	0	0%
Skin	0	0%
Spleen	0	0%
Intestinal mucosa	1.00	100%
Duodenum	1.00	100%
Upper Jejunum	1.00	100%
Lower Jejunum	1.00	100%
Upper Ileum	1.00	100%
Lower Ileum	1.00	100%
Cecum	0	0%
Colon ascendens	0	0%

Compound: 'Drug'

Metabolism -> Metabolizing Enzymes -> ENZ\_GI -> ENZ\_GI

Metabolite: In vitro clearance - First Order

Name	Value	Value Origin
Enzyme concentration	1.00000 $\mu\text{mol/l}$	
Specific clearance	1.00000 1/min	

Parameters used in simulations

CLspec/[Enzyme]	Value	Value Origin
	1.00000 l/ $\mu\text{mol/min}$	

Description:  
Metabolic enzyme activity is described as first order process. Specific clearance is calculated from specific rates determined in an in vitro assay.

Simulation: 'Oral100mg'

Absorption -> Specific intestinal permeability

Experiment	Permeability	Value Origin	Default
Calculated	...	Show Values	Publication-Thelen K, Co...
PI	...	3.11000E-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).

The first screenshot shows the 'Configure Simulation: Oral100mg' window. The 'Individual or Population' section has 'Man30' selected. The 'Compounds Selection' section has 'Drug' checked. The 'Model Settings' section has 'Standard model for small molecules' selected. A diagram at the bottom illustrates the compartments: Plasma, Interstitial, and Intracellular, with arrows indicating transport between them and a red blood cell (RBC) in the plasma.

The second screenshot shows the 'Configure Simulation: Oral100mg' window with the 'Calculation methods' section. The 'Partition coefficients' and 'Cellular permeabilities' are set to 'PK-Sim Standard'. The 'Parameter Alternatives' section shows a table with the following data:

Parameter	Alternative in compound
Solubility	Measurement
Lipophilicity	Measurement
Fraction unbound (plasma, reference value)	Measurement
Specific organ permeability	Calculated
Specific intestinal permeability	PI

The third screenshot shows the 'Simulation: Oral100mg' window. The 'Parameters' tab is active. The 'Intestinal solubility' table is displayed, showing the value for each compartment. The 'Rectum' compartment is highlighted in blue.

Compartment	Value	Value Origin	Favorites
Stomach	1000.00000 mg/l		
Duodenum	1000.00000 mg/l		
Upper Jejunum	1000.00000 mg/l		
Lower Jejunum	1000.00000 mg/l		
Upper Ileum	1000.00000 mg/l		
Lower Ileum	1000.00000 mg/l		
Cecum	1000.00000 mg/l		
Colon Ascendens	0 mg/l	Unknown	
Colon Transversum	0 mg/l	Unknown	
Colon Descendens	0 mg/l	Unknown	
Colon Sigmoid / D...	0 mg/l	Unknown	
Rectum	0 mg/l	Unknown	

# 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”

Parameter Identification: 'Parameter Identification 1' x

Parameters

Enter text to find

Organ Name

Simul...

Arterial Blood

Bone

Brain

Cecum

Colon Ascend

Colon Descend

Colon Sigmoid

Colon Transverse

Duodenum

Fat

Gonads

Add

Identification Parameters

Name	Start Value	Min. Value	Max. Value	Scaling	Use as Fac...	Fixed
Specific int...	3.11000E-...	0 cm/min	3.11000E-...	Linear		
CLspec/[Enzyme]	1.00000 l/μ...	0 l/μmol/min	10.00000 l/μ...	Linear		

Add

Simulation Parameters in CLspec/[Enzyme]

Simulation	Top Container	Organ	Name	Initial Value
Oral100mg	Drug-ENZ_GI...	Reaction	CLspec/[Enzyme]	1.00000 l/μmol/min

Add

Parameter Identification: 'Parameter Identification 1' x

Configuration

General

Transform data below LLOQ: Observed data and simulated data below LLOQ set to LLOQ

Remove data below LLOQ: Never

Algorithm: Levenberg - Marquardt

Calculate Sensitivity

Algorithm parameters:

Name	Value
Relative chi-square convergence criterion (ftol)	0.001
Relative parameter convergence criterion (xtol)	1E-06
Orthogonality convergence criterion (gtol)	1E-10
Initial step bound factor	100
Maximum number of iterations	200
Maximum number of function evaluations	0
Finite derivative step size	1E-09

Options

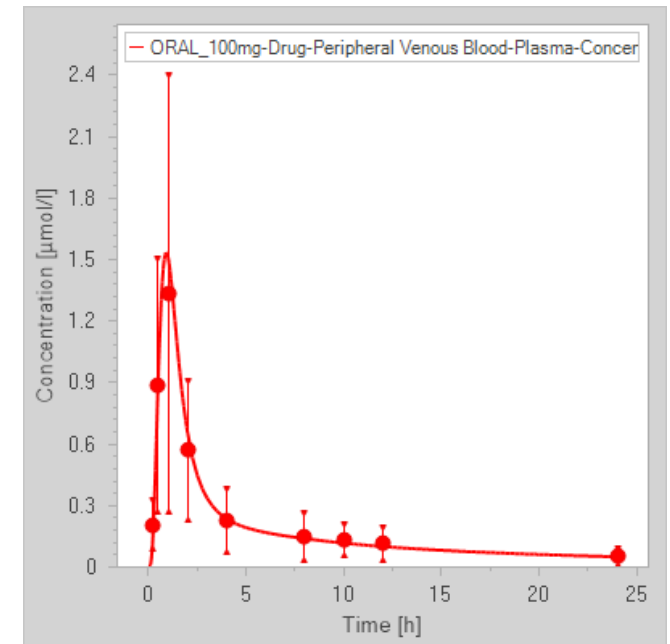
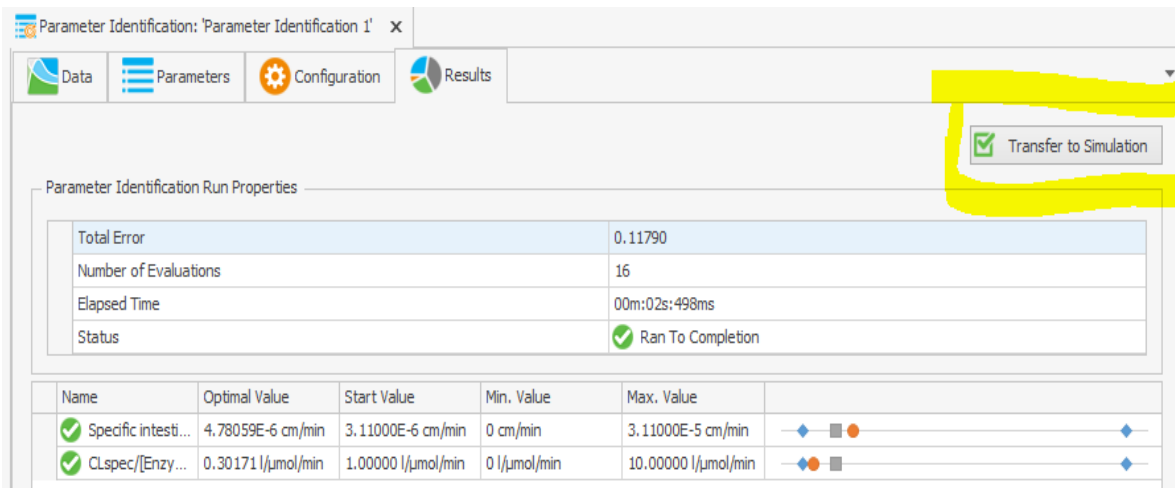
Standard

# 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)

The 'Create Population' dialog box is shown with the 'Demographics' tab selected. The 'Name' field is 'Test-POP'. The 'Based on individual' dropdown is set to 'Man30'. The 'Population' is 'European (ICRP, 2002)'. The 'Population Properties' section shows 'Number of individuals' as 100 and 'Proportion of females [%]' as 50. The 'Population Parameters Ranges' section shows a table with ranges for Age, Height, Weight, and BMI.

Parameter	from	to	unit
Age	20.00000	40.00000	year(s)
Height			cm
Weight			kg
BMI	19.00000	29.00000	kg/m <sup>2</sup>

The 'Create Population' dialog box is shown with the 'User Defined Variability' tab selected. The 'Name' field is 'Test-POP'. The 'Filter' section shows a tree view of physiological parameters. The 'Add' button is highlighted. The 'Remove' button is also visible. The 'Enzymes, Transporters and Binding Partners' section shows a table with 'ENZ\_GI' and 'ENZ\_LIV' entries. The 'Log Normal' distribution is selected for the 'ENZ\_GI' entry.

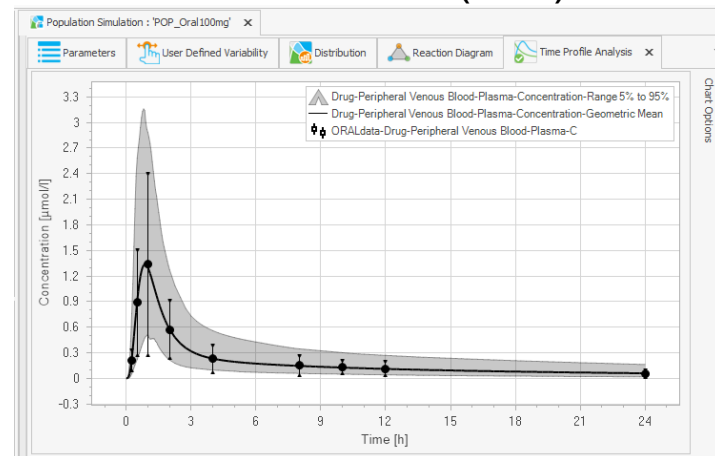
Name	Value	Value Origin
Mean	1.00000	μmol/l
Geometric Stan...	1.30000	

# 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.



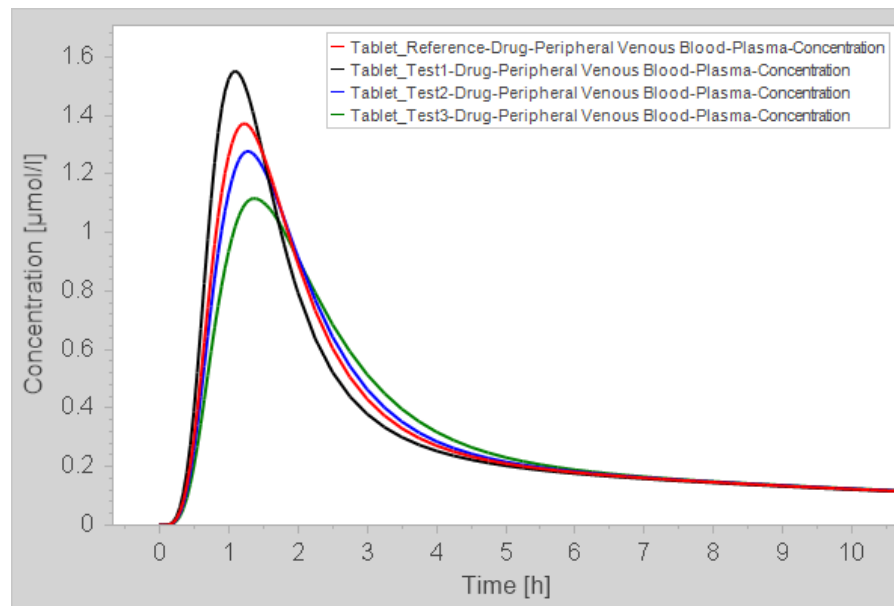
If time allows:

- 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

