

Step-by-step guide for case study “Oral drug absorption modeling in PK-Sim”

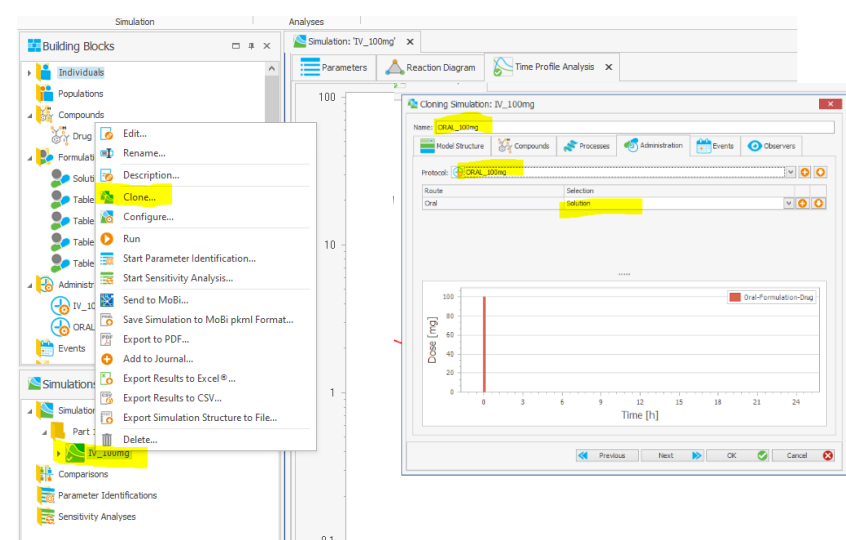
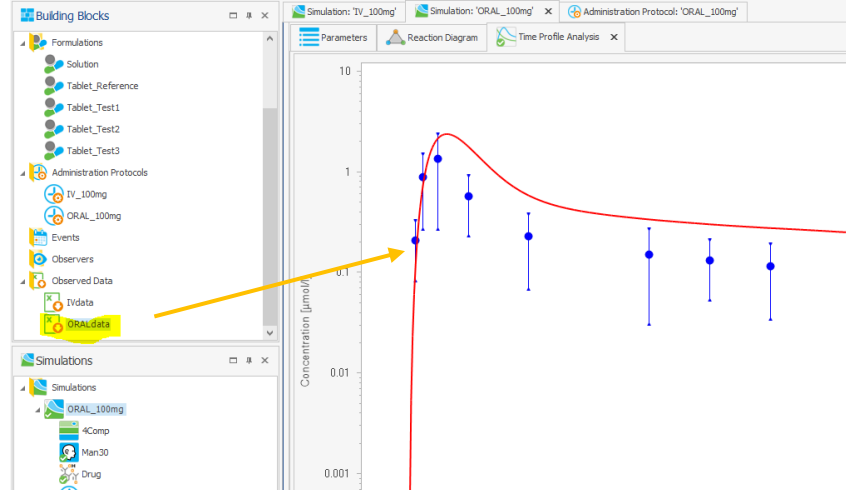
In this walkthrough guide basic operations and usage of PK-Sim are not show explicitly as there are excellent YouTube videos from scientist of [Clinical Pharmacy Saarland University](#) and detailed documentations on [Open Systems Pharmacology](#)

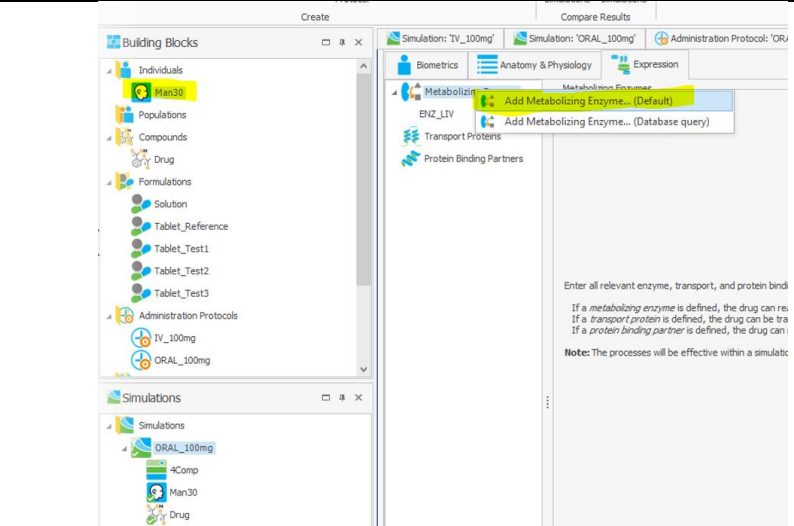
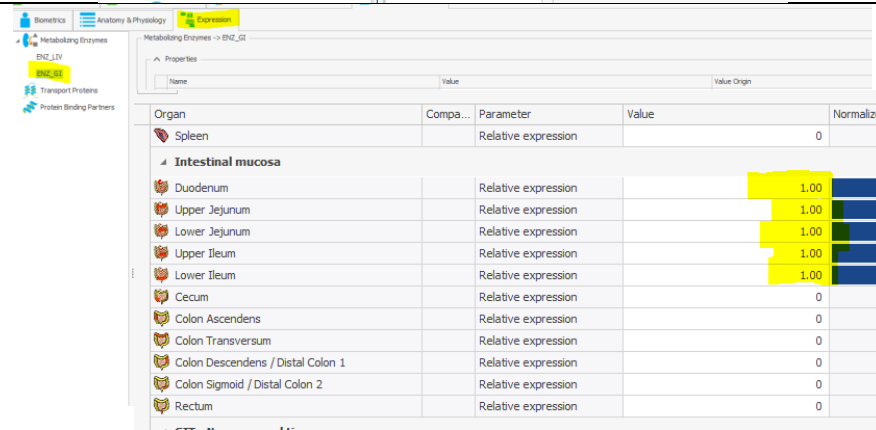
In this content overview links are pointing to these YouTube videos.

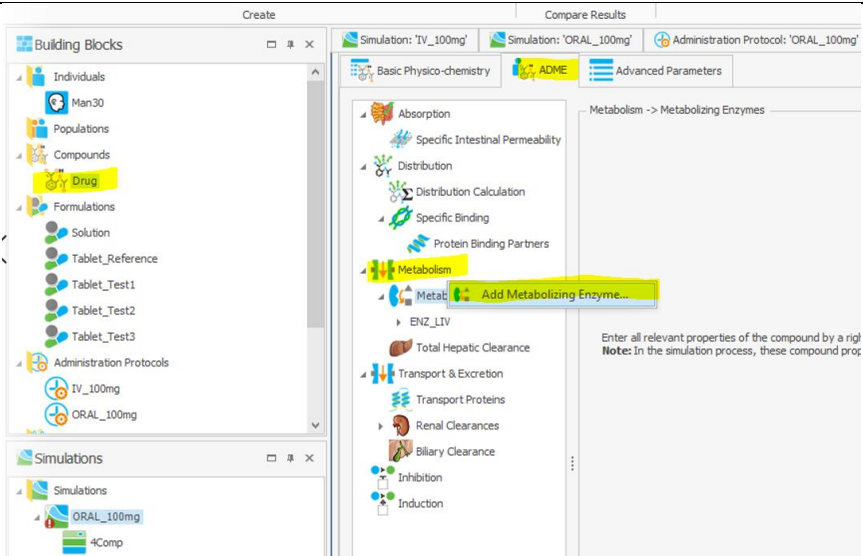
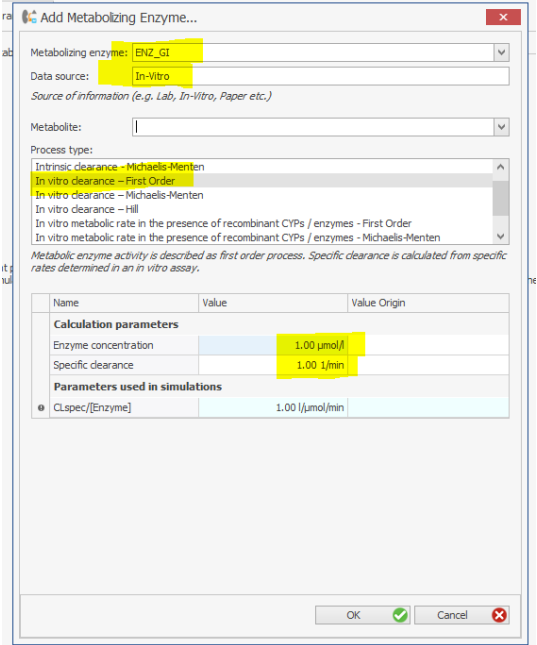
- Generate Healthy [individual](#)
- Generate [compounds](#) (from template DB)
- Set up [administration](#) scenarios
- Import [observed data](#)
- Build population and run [simulations](#) and compare to observed data
- Compare Simulations

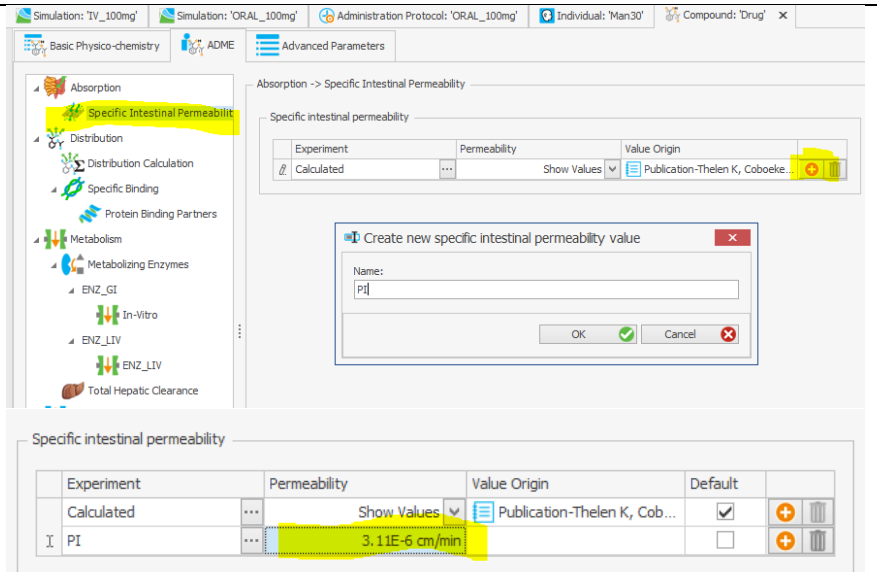
Detailed Step-by-Step

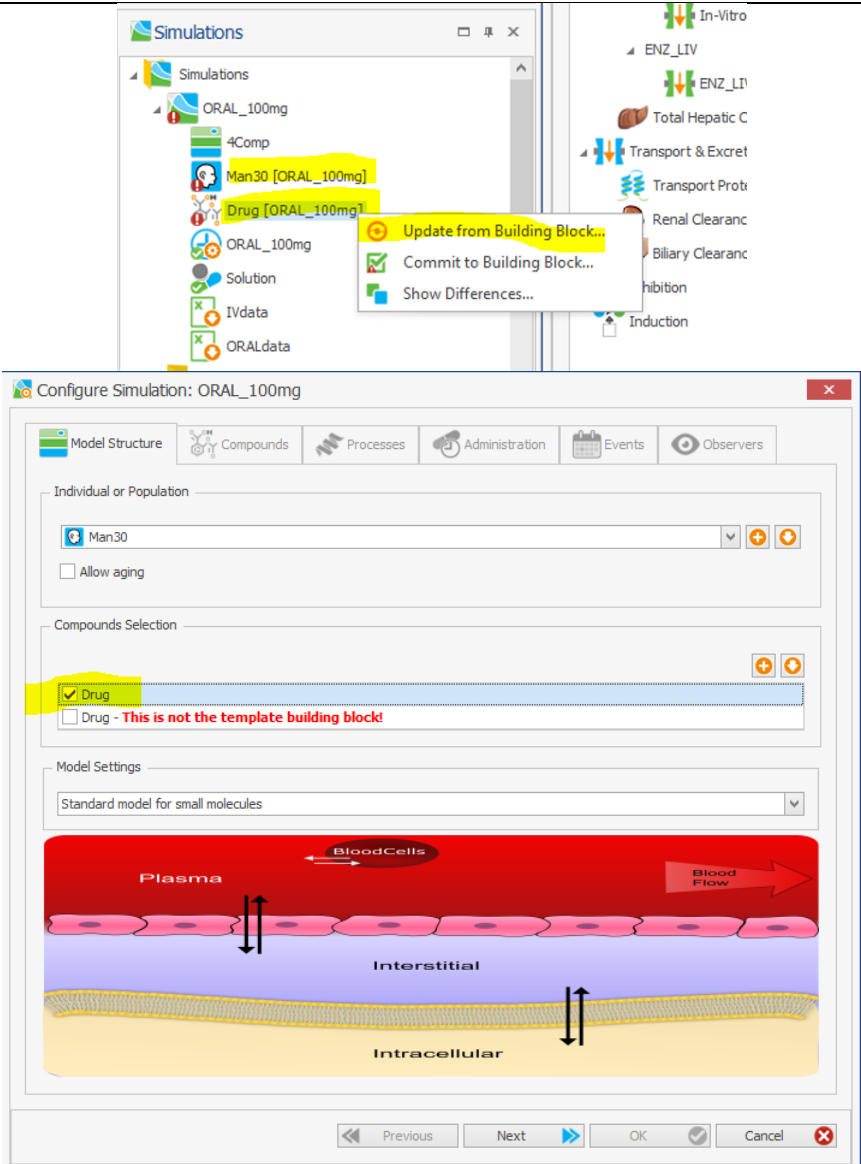
File	Step	action	comment	image
(1) Establish oral absorption model				

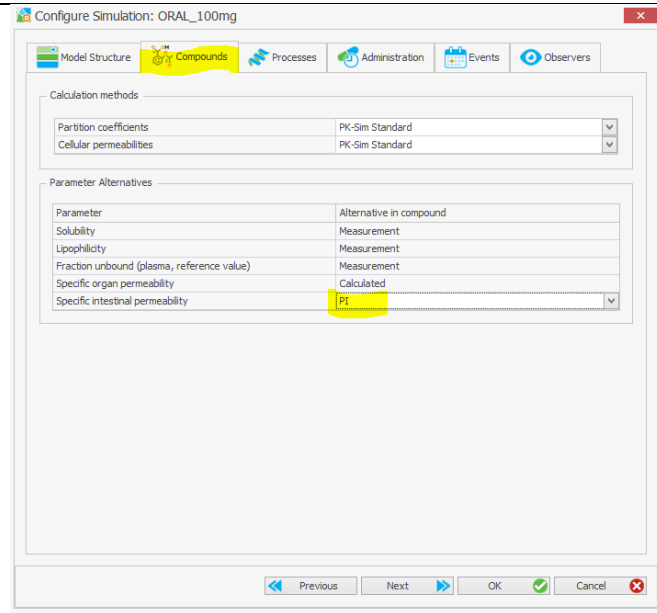
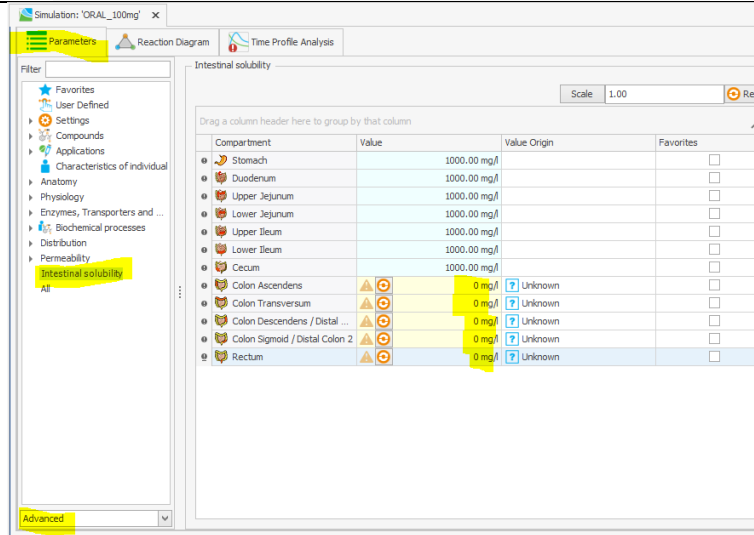
File	Step	action	comment	image
Handson II-Absorption_1	1.a	<i>Clone compound</i>	Clone simulation “IV_100mg”, name “ORAL_100mg” Select Administration protocol “ORAL_100mg” and formulation “Solution”. And run.	
	1.b	<i>Observe data</i>	Remove “IVdata” and add “ORALdata”	

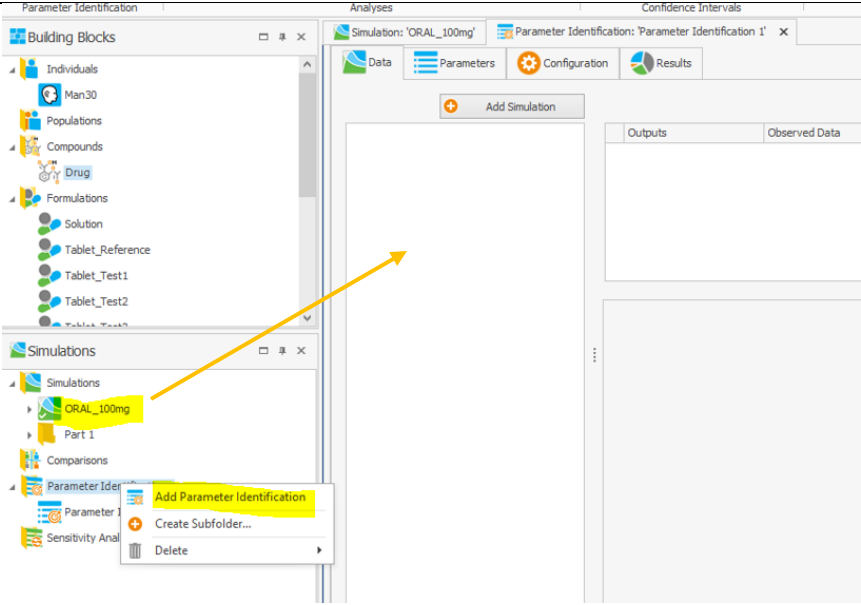
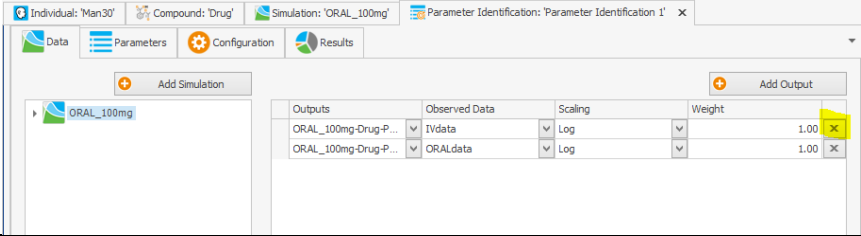
File	Step	action	comment	image
	2.a	Add GI enzyme in individual	Add “ENZ_GI” under Expression tab of individual Man30	
	2.a	Add GI enzyme in individual	Add relative expression = 1 in small intestine mucosa and keep other inputs as default	

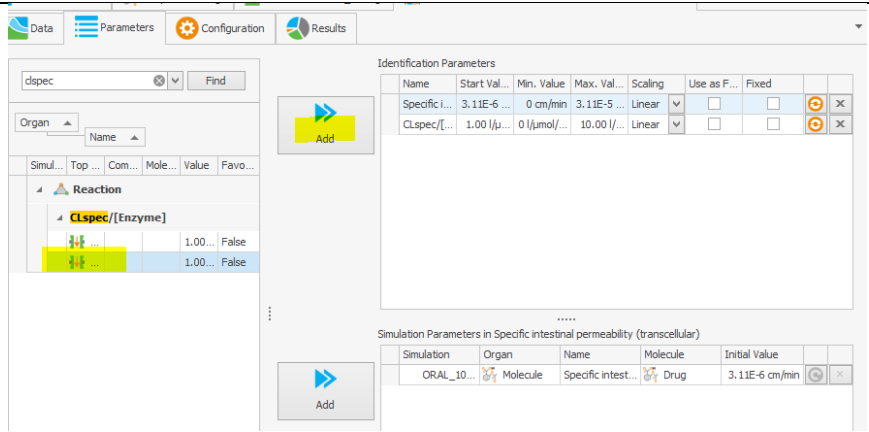
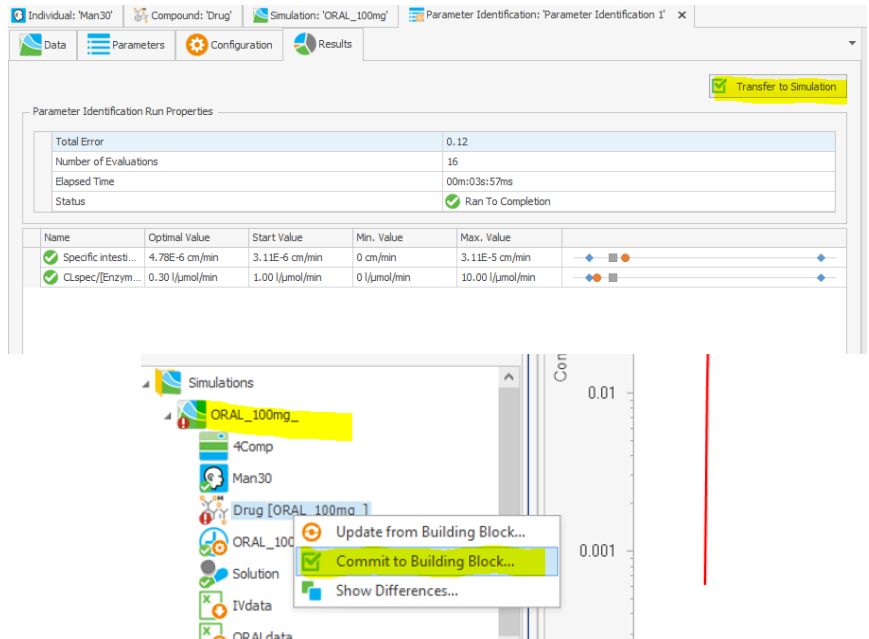
File	Step	action	comment	image
	2.b	Add enzyme in compound	Add “Metabolizing enzyme” for ENZ_GI in compound Drug under tab ADME	
	2.b	Add enzyme in compound	Fill in, ENZ_GI, in vitro, CL-first other, Enzyme concentration and specific clearance 1 μmol	

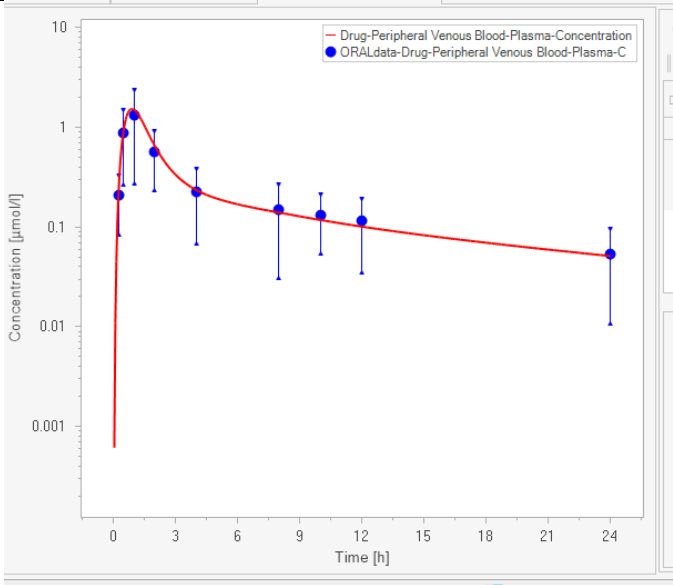
File	Step	action	comment	image												
Steps up and until this point are given in Handson II-Absorption_2	2.b	Add enzyme in compound	Create new “specific intestinal permeability value” (PI) set to calculate value (3.11E-6 cm/min)	 <p>The screenshot displays the 'Specific Intestinal Permeability' configuration window. On the left, a tree view shows the 'Specific Intestinal Permeability' node under 'Absorption'. The main panel shows the 'Specific intestinal permeability' section with a table of values. A dialog box titled 'Create new specific intestinal permeability value' is open, showing the name 'PI'. Below the dialog, a table lists the permeability values:</p> <table><tr><th>Experiment</th><th>Permeability</th><th>Value Origin</th><th>Default</th></tr><tr><td>Calculated</td><td>3.11E-6 cm/min</td><td>Publication-Thelen K, Coboeke</td><td><input checked="" type="checkbox"/></td></tr><tr><td>PI</td><td>3.11E-6 cm/min</td><td></td><td><input type="checkbox"/></td></tr></table>	Experiment	Permeability	Value Origin	Default	Calculated	3.11E-6 cm/min	Publication-Thelen K, Coboeke	<input checked="" type="checkbox"/>	PI	3.11E-6 cm/min		<input type="checkbox"/>
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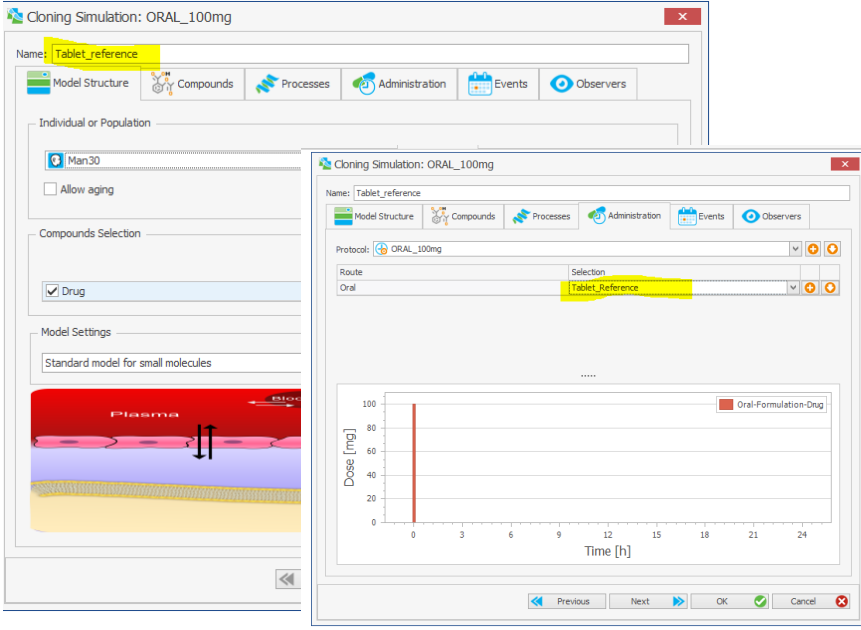
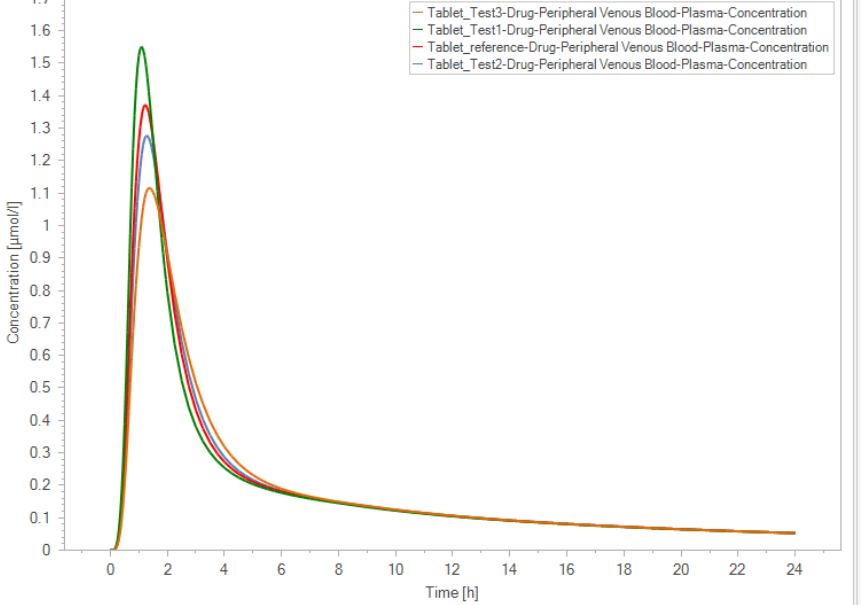
File	Step	action	comment	image
	3.a	<i>Simulate oral model performance</i>	Update “Man30” and “Drug” from Building Block and Select the “Drug” in automatically opened configuration window	 <p>The image shows two overlapping windows from a pharmacokinetic modeling software. The top window, titled 'Simulations', displays a hierarchical tree of simulation components. In this tree, 'Man30 [ORAL_100mg]' and 'Drug [ORAL_100mg]' are highlighted with yellow boxes. A context menu is open over the 'Drug' entry, with the option 'Update from Building Block...' also highlighted in yellow. The bottom window, titled 'Configure Simulation: ORAL_100mg', is a configuration dialog. It has tabs for 'Model Structure', 'Compounds', 'Processes', 'Administration', 'Events', and 'Observers'. The 'Compounds' tab is active. Under 'Individual or Population', 'Man30' is selected. Under 'Compounds Selection', the 'Drug' checkbox is checked and highlighted with a yellow box, while the option 'Drug - This is not the template building block!' is unchecked. Below this, the 'Model Settings' section shows 'Standard model for small molecules' selected. At the bottom of the dialog is a schematic diagram of a three-compartment model: 'Plasma' (top, red), 'Interstitial' (middle, blue), and 'Intracellular' (bottom, yellow). Arrows indicate 'Blood Cells' and 'Blood Flow' between the plasma and interstitial spaces, and bidirectional exchange between the interstitial and intracellular spaces. Navigation buttons at the bottom include 'Previous', 'Next', 'OK', and 'Cancel'.</p>

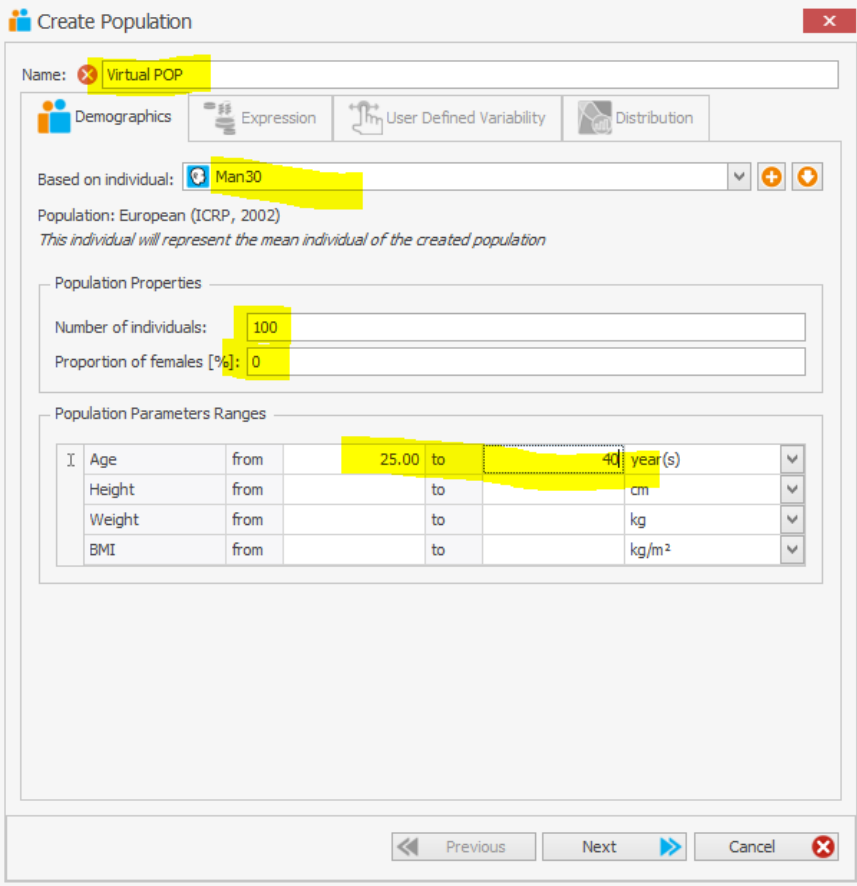
File	Step	action	comment	image
	3.b	<i>Simulate oral model performance</i>	1. Use new permeability value (PI) form drop-down	
Steps up and until here are filed in Handson II-Absorption_3.pksim5	3.b	<i>Simulate oral model performance</i>	Exclude absorption from colon ascendens –rectum e.g. by setting intestinal solubility (visible in “Advanced” view-mode) to 0 in these compartments	

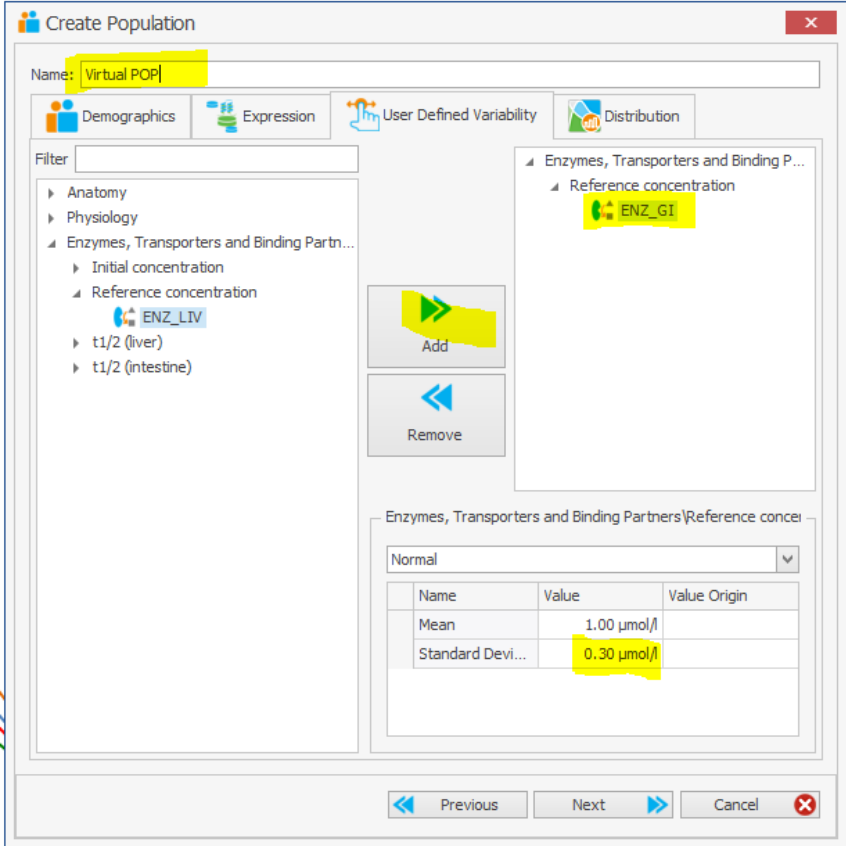
File	Step	action	comment	image
	4a	<i>Parameter Identification</i>	Create a parameter Identification and include "ORAL_100mg"	
	4a	<i>Parameter Identification</i>	Delete IV data	

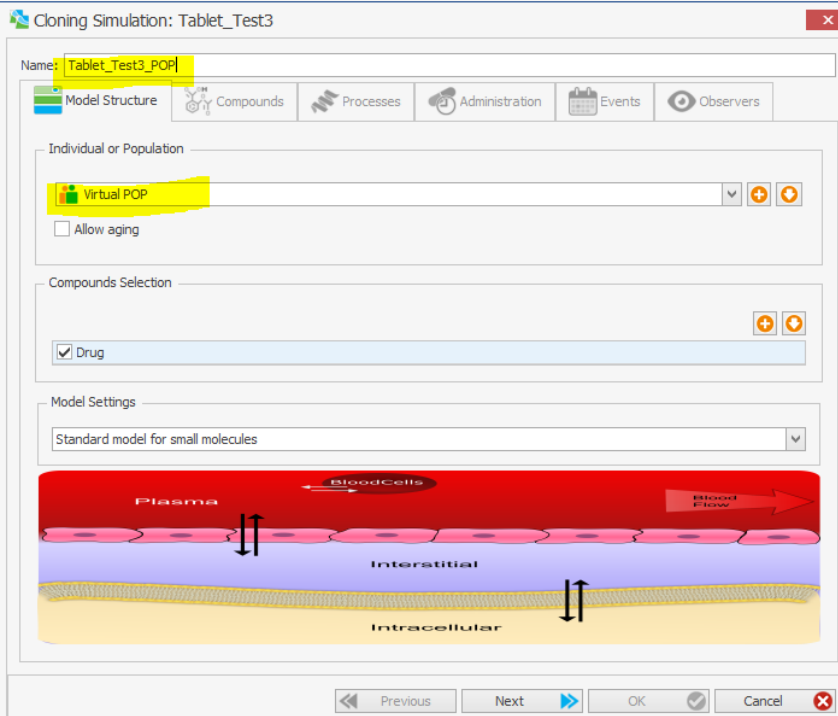
File	Step	action	comment	image
	4a	Parameter Identification	Select “Specific intestinal permeability (transcellular)” and “CLspec/[Enzyme]” for (only!) ENZ_GI and Run	
	4b	Transfer Parameter Identification	Transfer to Simulations from “Results” and “Commit to building block”	

File	Step	action	comment	image
Steps up and until now are saved in Handson II-Absorption_4.pksim5	5.a	<i>Look at results</i>		
(4) Formulation performance in virtual populations				
	6.a	<i>Set up simulations for different formulations for typical individual</i>	Clone simulation “ORAL_100mg” and name “Tablet_Reference” and select formulation “Tablet_Reference”. Remove ORALdata observations.	

File	Step	action	comment	image
				
<p>Steps up and until now are saved in Handson II-Absorption_5.pksim5</p>	<p>6.b</p>	<p><i>Set up simulations for different formulations for typical individual</i></p>	<p>Clone simulation “Tablet_Reference” to create simulations “Tablet_Test1”, “Tablet_Test2” and “Tablet_Test3” and run each simulation. Click on Compare Results in the “Run & Analyze” tab and drag Simulations of Tablets there.</p>	

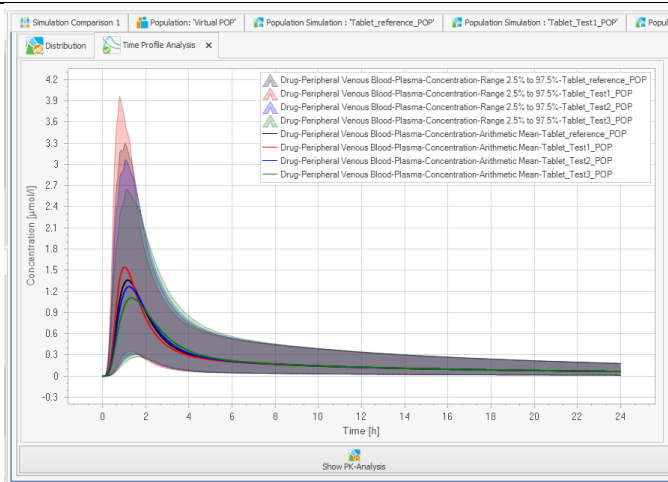
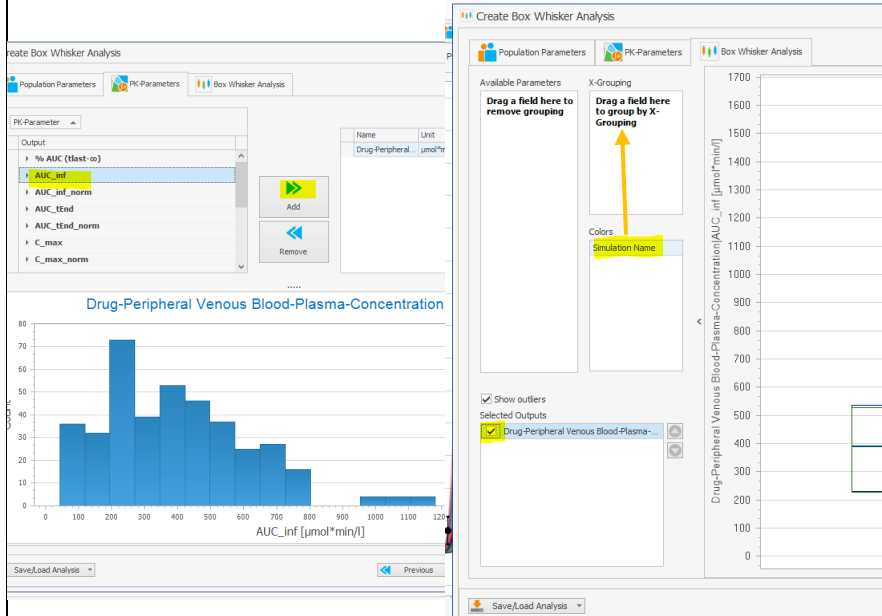
File	Step	action	comment	image
	7.a	Create a virtual population	Create virtual population based on "Man30", e.g., age 25-40 , 100% men, n=100	

File	Step	action	comment	image
	7.b	Add variability	Add under “User Defined Variability” ENZ_GI and define variability with a SD of 0.3.	

File	Step	action	comment	image
	8	<i>Clone tablet simulations</i>	Clone tablet simulations, add suffix “_POP”, and replace “Man30” with created virtual population for all tablet forms	

File	Step	action	comment	image																																																				
	9	Run simulations	Run all formulations and add the 95% quantile and add AUC_inf and C_max for PK-parameters check.	<div><div><div>Create Time Profile Analysis</div><div><div>Output</div><div>Population Parameters</div><div>PK-Parameters</div><div>Time Profile Analysis</div></div><div><div>Organ</div><div><table><tr><th>Compartment</th><th>Molecule</th><th>Name</th></tr><tr><td>Peripheral Venous Blood</td><td></td><td></td></tr><tr><td>Plasma</td><td>Drug</td><td>Concentration</td></tr></table></div><div><div>Add</div><div>Remove</div></div><div><div>Time unit: h</div><div><table><tr><th>Name</th><th>Unit</th><th>Scaling</th><th>Color</th></tr><tr><td>Drug-Perip...</td><td>µmol/l</td><td>Linear</td><td></td></tr></table></div><div><div>Output: Select distribution statistics for display</div><div><table><tr><th>Selected</th><th>Name</th><th>Line Style</th></tr><tr><td><input type="checkbox"/></td><td>Max</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>Median</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>Range 5% to 95%</td><td>Solid</td></tr><tr><td><input checked="" type="checkbox"/></td><td>Range 2.5% to 97.5%</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>10th Percentile</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>25th Percentile</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>90th Percentile</td><td>Solid</td></tr></table></div></div><div><div>Save/Load Analysis</div><div>Previous</div><div>Next</div><div>Cancel</div></div></div></div><div><div>Create Time Profile Analysis</div><div><div>Output</div><div>Population Parameters</div><div>PK-Parameters</div><div>Time Profile Analysis</div></div><div><div>PK-Parameter</div><div><div>Output</div><div><table><tr><td>% AUC (last-∞)</td></tr><tr><td>AUC_inf</td></tr><tr><td>Drug-Peripheral Venous Blood-Plasma-Concentration</td></tr><tr><td>AUC_inf_norm</td></tr><tr><td>AUC_tEnd</td></tr><tr><td>AUC_tEnd_norm</td></tr><tr><td>C_max</td></tr></table></div><div><div>Add</div><div>Remove</div></div></div><div><div>Create Grouping</div><div><table><tr><th>Name</th><th>Unit</th></tr><tr><td colspan="2">Add one or several PK-Parameters, change name or unit by clicking into the respective column</td></tr></table></div></div><div><div>Organism PeripheralVenousBlood Drug Plasma (Peripheral Venous Blood)</div><div><div>Count</div><div></div></div><div><div>Save/Load Analysis</div><div>Previous</div><div>Next</div><div>Cancel</div></div></div></div></div></div></div>	Compartment	Molecule	Name	Peripheral Venous Blood			Plasma	Drug	Concentration	Name	Unit	Scaling	Color	Drug-Perip...	µmol/l	Linear		Selected	Name	Line Style	<input type="checkbox"/>	Max	Solid	<input type="checkbox"/>	Median	Solid	<input type="checkbox"/>	Range 5% to 95%	Solid	<input checked="" type="checkbox"/>	Range 2.5% to 97.5%	Solid	<input type="checkbox"/>	10th Percentile	Solid	<input type="checkbox"/>	25th Percentile	Solid	<input type="checkbox"/>	90th Percentile	Solid	% AUC (last-∞)	AUC_inf	Drug-Peripheral Venous Blood-Plasma-Concentration	AUC_inf_norm	AUC_tEnd	AUC_tEnd_norm	C_max	Name	Unit	Add one or several PK-Parameters, change name or unit by clicking into the respective column	
Compartment	Molecule	Name																																																						
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File	Step	action	comment	image
	10.a	Visualize results	Make a simulation comparison of all Tablet forms under “Run & Analyze” and then “Compare Results”. Select all pop tablet formulations. Select the 95% quantile under output and add AUC_inf and C_max under PK-Parameters.	<p>The image displays two screenshots from the 'Create Time Profile Analysis' software interface.</p> <p>The top screenshot shows the 'Organ' tab. On the left, a list of compartments includes 'Peripheral Venous Blood' and 'Plasma'. On the right, a table lists parameters for 'Drug-Perip...'. The 'Range 2.5% to 97.5%' row is highlighted in yellow.</p> <p>The bottom screenshot shows the 'PK-Parameter' tab. On the left, a list of parameters includes 'AUC_inf' and 'C_max', both highlighted in yellow. On the right, a table lists parameters for 'Drug-Peripheral Venous...'. Below the tables, a histogram titled 'Drug-Peripheral Venous Blood-Plasma-Concentration AUC_inf' shows the distribution of AUC values. The x-axis is labeled 'AUC_inf [μmol*min/l]' and the y-axis is labeled 'Count'.</p>

File	Step	action	comment	image
	10.a	Visualize results	Time Profile comparison	
	10.b	Visualize results	Make a Box Whisker comparison for AUC_inf by clicking on Box Whisker under analyze. Add AUC_inf and drag Simulation name to X-grouping under Box Whisker Analysis.	

File	Step	action	comment	image
All the steps are summed in file Handson II-Absorption_6.pksim5	10.b	<i>Visualize results</i>	Repeat for C_max	