

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

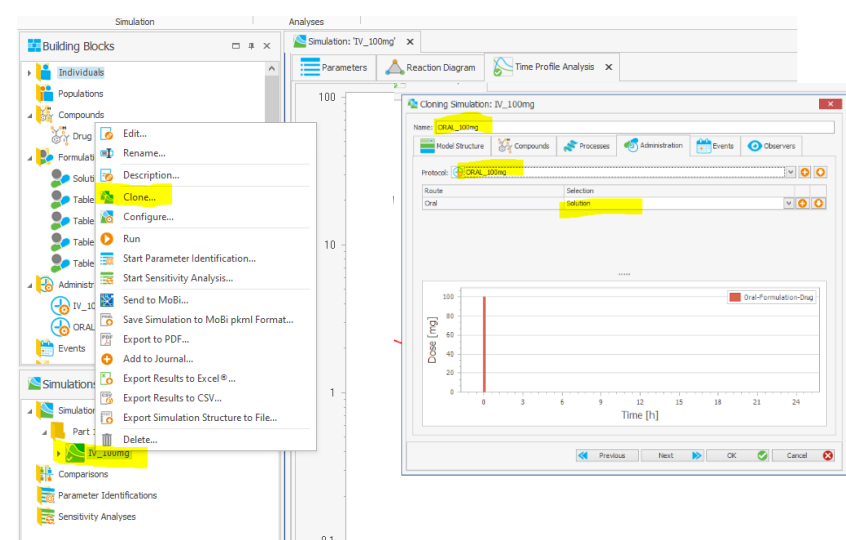
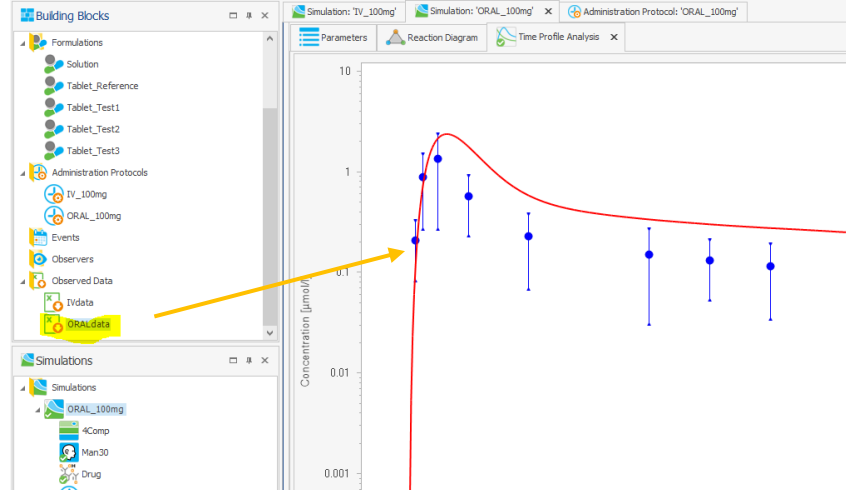
In this walkthrough guide basic operations and usage of PK-Sim are not show explicitly as there are excellent YouTube videos from scientist of [Clinical Pharmacy Saarland University](#) and detailed documentations on [Open Systems Pharmacology](#)

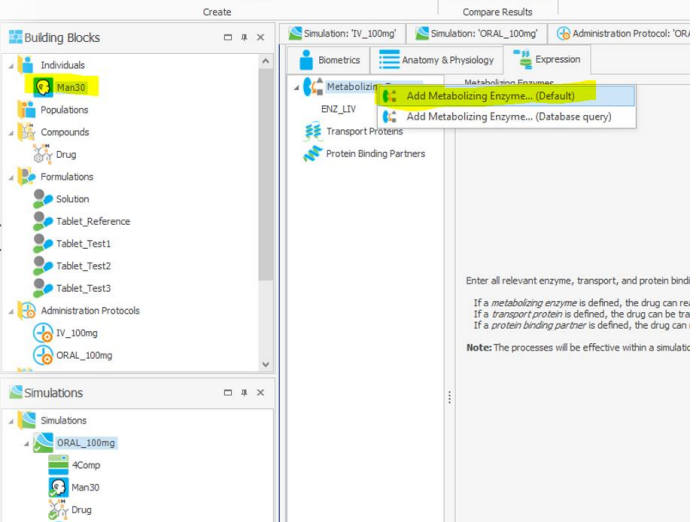
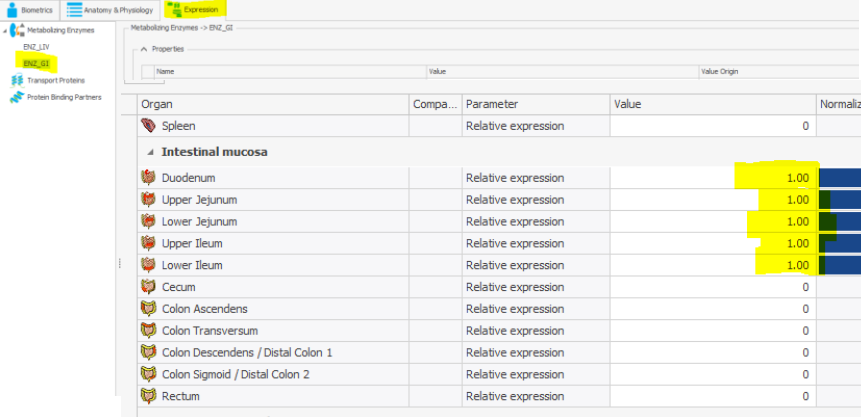
In this content overview links are pointing to these YouTube videos.

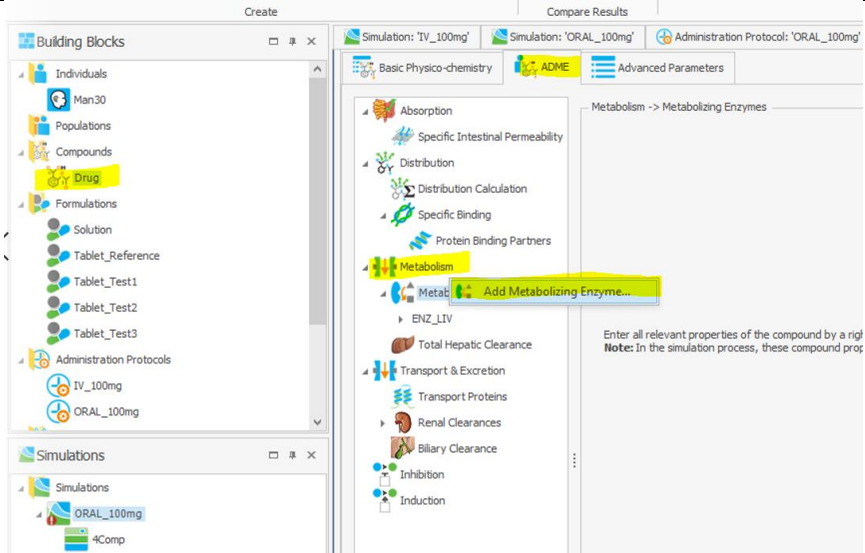
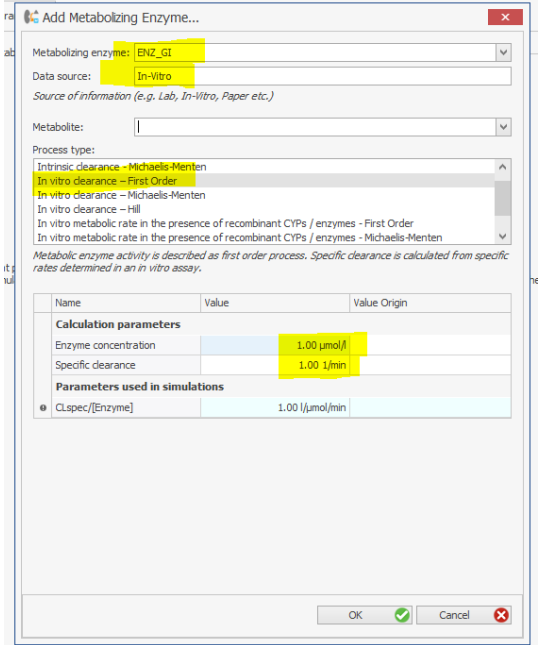
- Generate Healthy [individual](#)
- Generate [compounds](#) (from template DB)
- Set up [administration](#) scenarios
- Import [observed data](#)
- Build population and run [simulations](#) and compare to observed data
- Compare Simulations

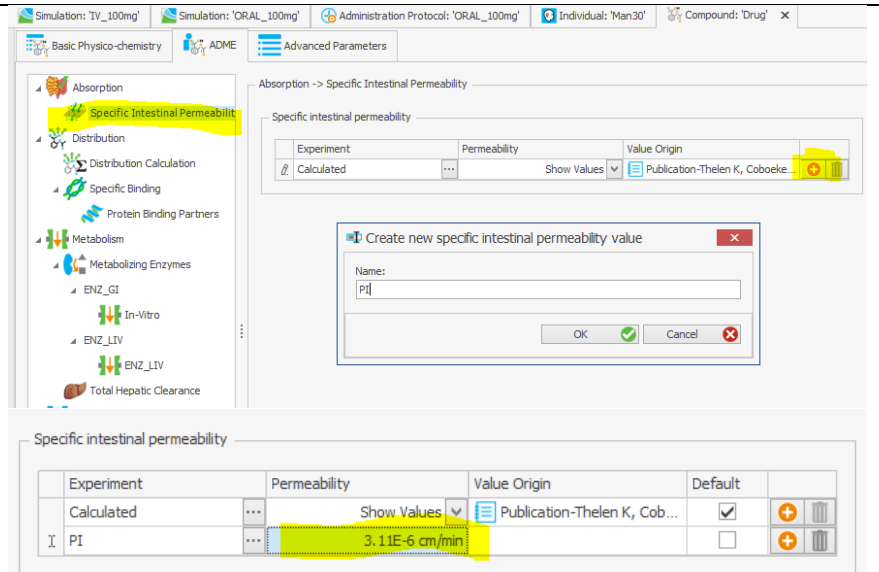
Detailed Step-by-Step

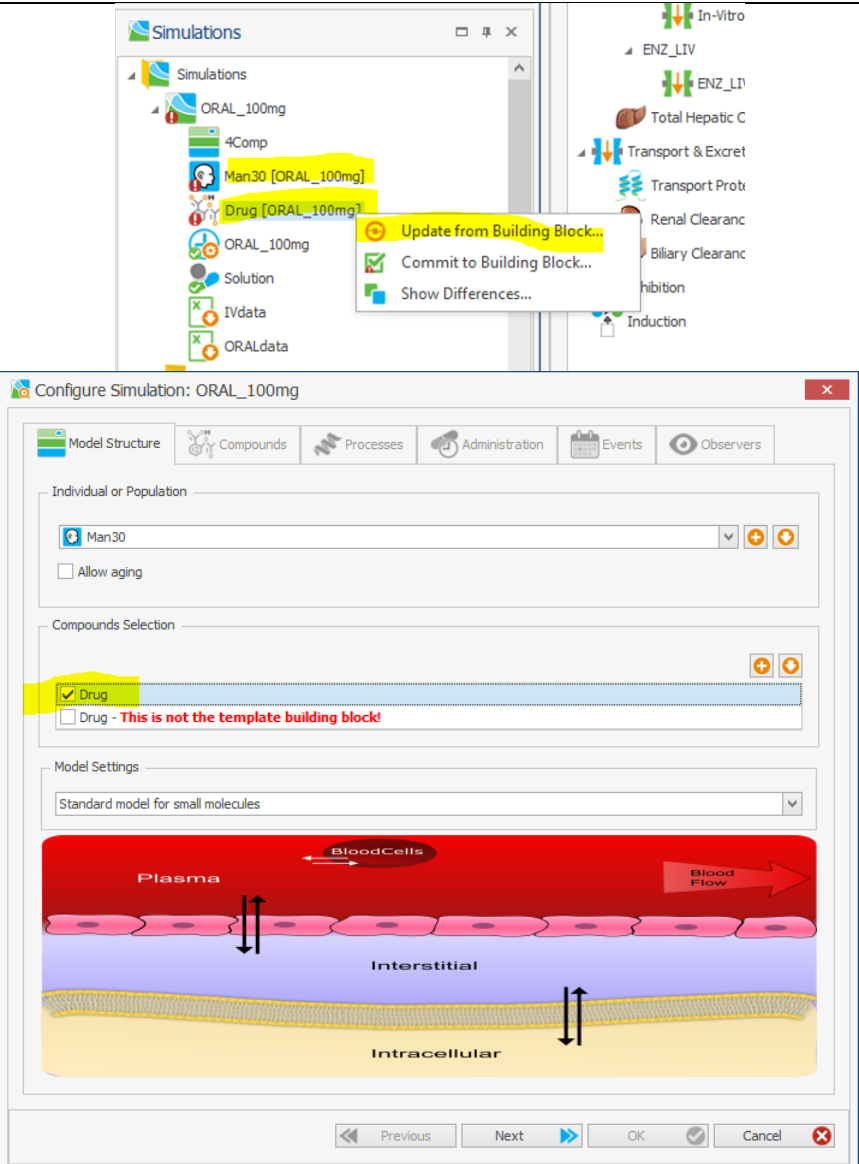
File	Step	action	comment	image
(1) Establish oral absorption model				

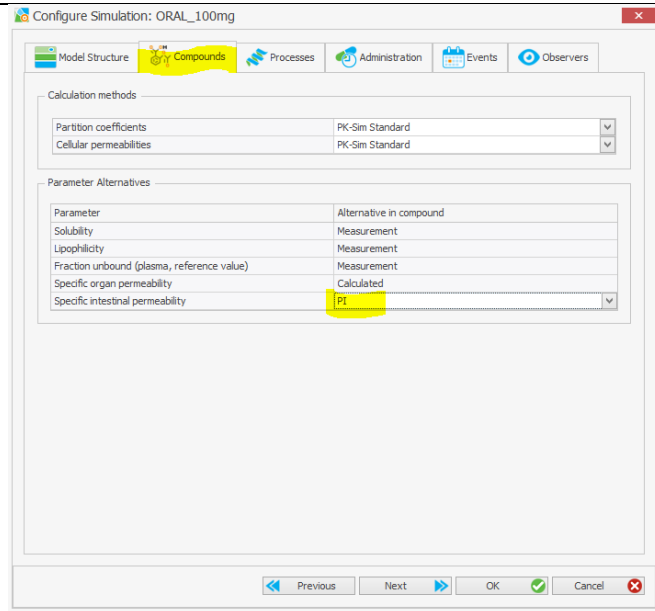
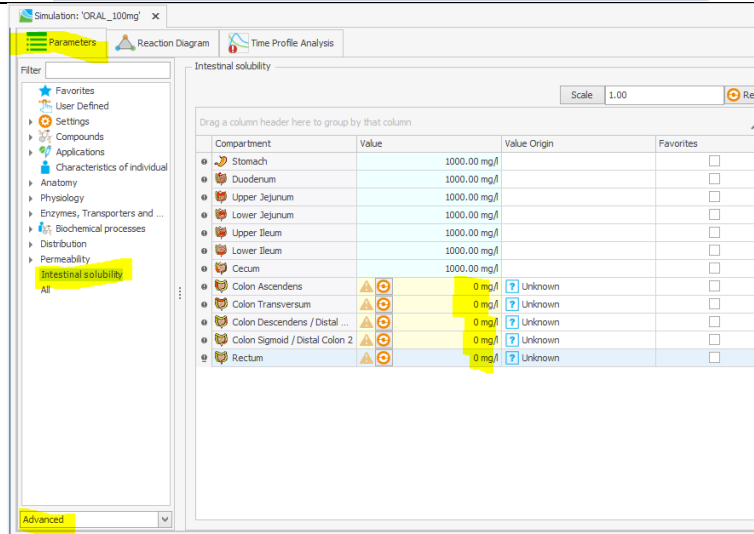
File	Step	action	comment	image
Handson II-Absorption_1.pksim5	1.a	<i>Clone compound</i>	Clone simulation “IV_100mg”, name “ORAL_100mg” Select Administration protocol “ORAL_100mg” and formulation “Solution”. And run.	
	1.b	<i>Observe data</i>	Remove “IVdata” and add “ORALdata”	

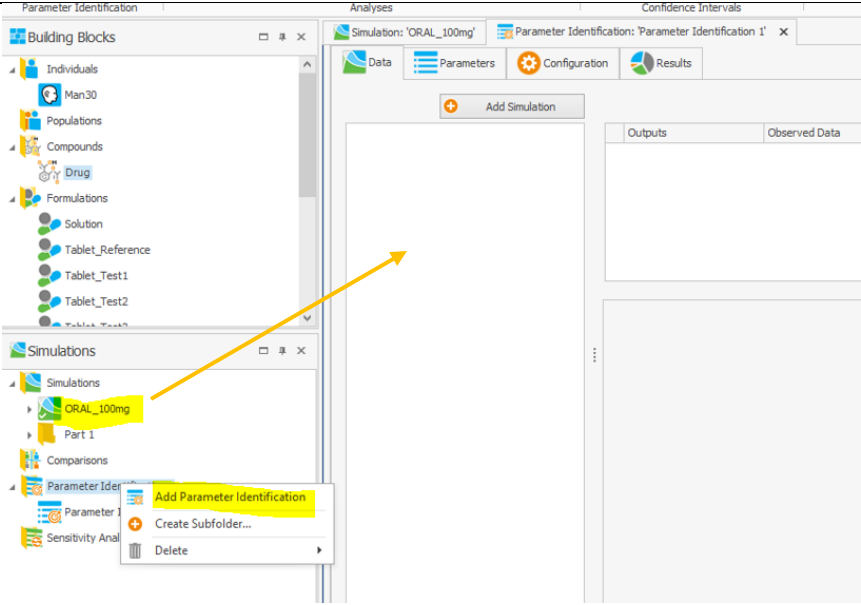
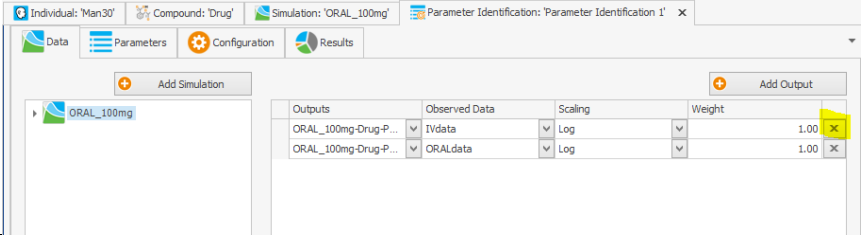
File	Step	action	comment	image																																																																						
	2.a	Add GI enzyme in individual	Add “ENZ_GI” under Expression tab of individual Man30	 <p>Building Blocks</p> <ul style="list-style-type: none"> Individuals <ul style="list-style-type: none"> Man30 Populations Compounds <ul style="list-style-type: none"> Drug Formulations <ul style="list-style-type: none"> Solution Tablet_Reference Tablet_Test1 Tablet_Test2 Tablet_Test3 Administration Protocols <ul style="list-style-type: none"> IV_100mg ORAL_100mg <p>Simulations</p> <ul style="list-style-type: none"> Simulations <ul style="list-style-type: none"> ORAL_100mg 4Comp Man30 Drug <p>Expression</p> <ul style="list-style-type: none"> Metabolizing Enzymes <ul style="list-style-type: none"> ENZ_GI ENZ_LIV Transport Proteins Protein Binding Partners <p>Enter all relevant enzyme, transport, and protein bind</p> <p>If a <i>metabolizing enzyme</i> is defined, the drug can be re</p> <p>If a <i>transport protein</i> is defined, the drug can be tra</p> <p>If a <i>protein binding partner</i> is defined, the drug can</p> <p>Note: The processes will be effective within a simulati</p>																																																																						
	2.a	Add GI enzyme in individual	Add relative expression = 1 in small intestine mucosa and keep other inputs as default	 <p>Metabolizing Enzymes -> ENZ_GI</p> <table border="1"> <thead> <tr> <th>Organ</th> <th>Compa...</th> <th>Parameter</th> <th>Value</th> <th>Normalized</th> </tr> </thead> <tbody> <tr> <td>Spleen</td> <td></td> <td>Relative expression</td> <td>0</td> <td></td> </tr> <tr> <td colspan="5">Intestinal mucosa</td> </tr> <tr> <td>Duodenum</td> <td></td> <td>Relative expression</td> <td>1.00</td> <td></td> </tr> <tr> <td>Upper Jejunum</td> <td></td> <td>Relative expression</td> <td>1.00</td> <td></td> </tr> <tr> <td>Lower Jejunum</td> <td></td> <td>Relative expression</td> <td>1.00</td> <td></td> </tr> <tr> <td>Upper Ileum</td> <td></td> <td>Relative expression</td> <td>1.00</td> <td></td> </tr> <tr> <td>Lower Ileum</td> <td></td> <td>Relative expression</td> <td>1.00</td> <td></td> </tr> <tr> <td>Cecum</td> <td></td> <td>Relative expression</td> <td>0</td> <td></td> </tr> <tr> <td>Colon Ascendens</td> <td></td> <td>Relative expression</td> <td>0</td> <td></td> </tr> <tr> <td>Colon Transversum</td> <td></td> <td>Relative expression</td> <td>0</td> <td></td> </tr> <tr> <td>Colon Descendens / Distal Colon 1</td> <td></td> <td>Relative expression</td> <td>0</td> <td></td> </tr> <tr> <td>Colon Sigmoid / Distal Colon 2</td> <td></td> <td>Relative expression</td> <td>0</td> <td></td> </tr> <tr> <td>Rectum</td> <td></td> <td>Relative expression</td> <td>0</td> <td></td> </tr> </tbody> </table>	Organ	Compa...	Parameter	Value	Normalized	Spleen		Relative expression	0		Intestinal mucosa					Duodenum		Relative expression	1.00		Upper Jejunum		Relative expression	1.00		Lower Jejunum		Relative expression	1.00		Upper Ileum		Relative expression	1.00		Lower Ileum		Relative expression	1.00		Cecum		Relative expression	0		Colon Ascendens		Relative expression	0		Colon Transversum		Relative expression	0		Colon Descendens / Distal Colon 1		Relative expression	0		Colon Sigmoid / Distal Colon 2		Relative expression	0		Rectum		Relative expression	0	
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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.pksim5	3	Add specific intestinal permeability	Create new “specific intestinal permeability value” (PI) set to calculate value (3.11E-6 cm/min)	 <p>The screenshot shows the PK-Sim software interface. The left sidebar contains a tree view with categories like Absorption, Distribution, Specific Binding, Protein Binding Partners, Metabolism, and Metabolizing Enzymes. The 'Specific Intestinal Permeability' node is highlighted. The main window displays the 'Absorption -> Specific Intestinal Permeability' settings. A table at the bottom 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>...</td><td>Show Values</td><td>Publication-Thelen K, Coboeke...</td></tr><tr><td>I PI</td><td>...</td><td>3.11E-6 cm/min</td><td></td></tr></table>	Experiment	Permeability	Value Origin	Default	Calculated	...	Show Values	Publication-Thelen K, Coboeke...	I PI	...	3.11E-6 cm/min	
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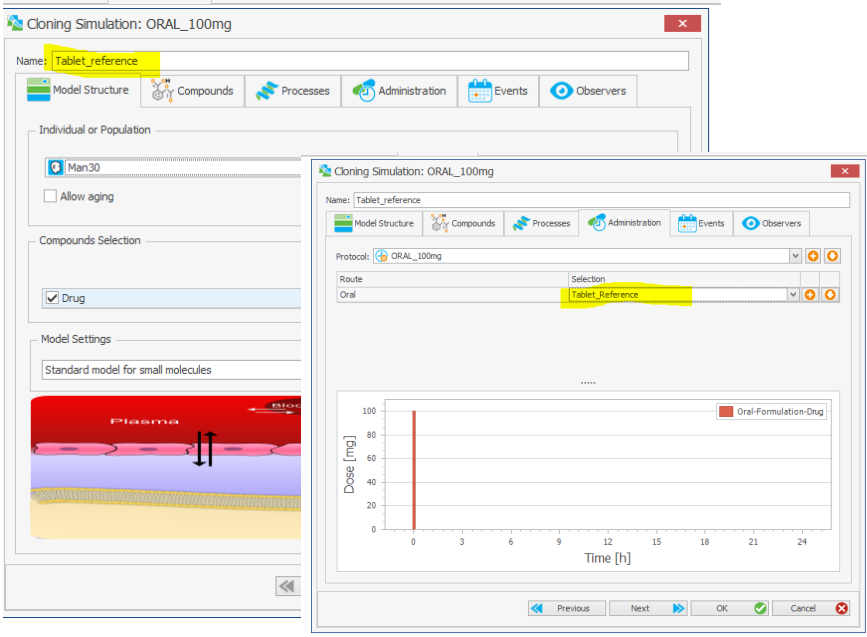
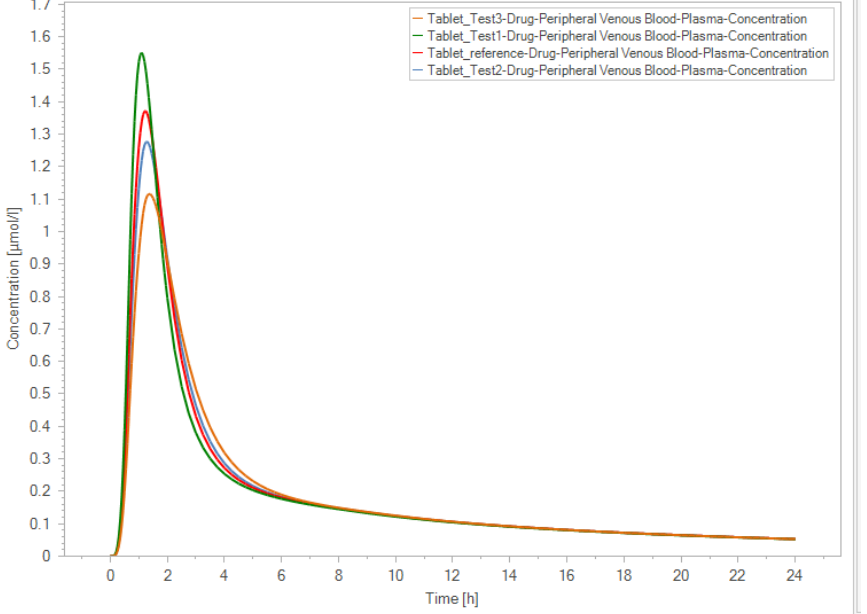
File	Step	action	comment	image
	4.a	<i>Simulate oral model performance</i>	Update “Man30” and “Drug” from Building Block and Select the “Drug” in automatically opened configuration window	

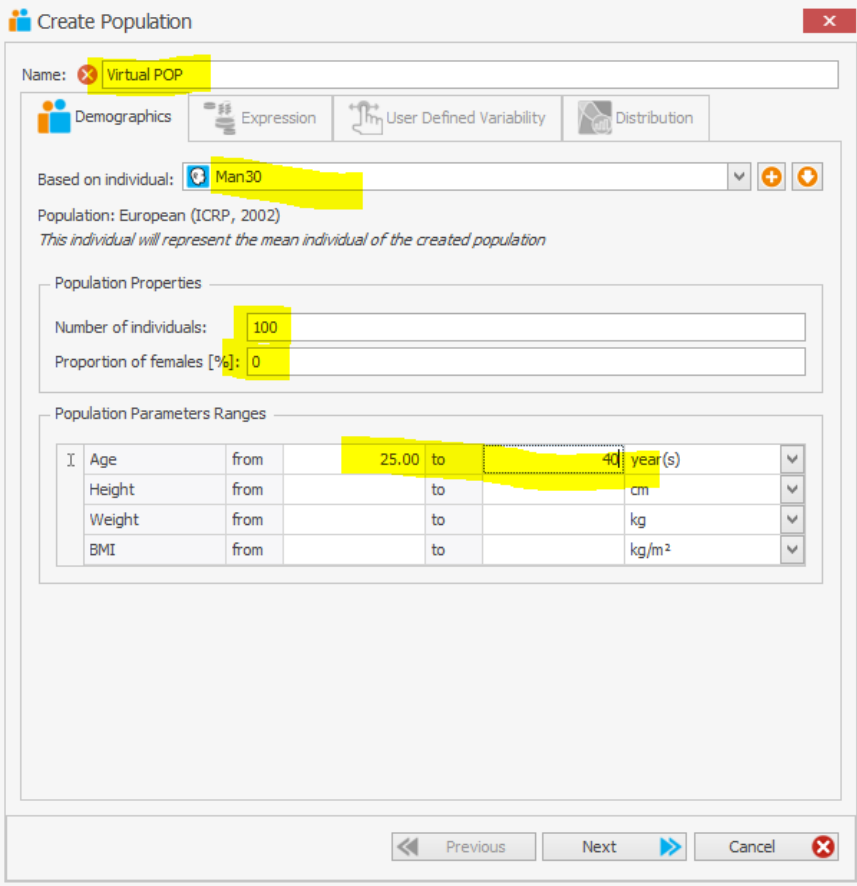
File	Step	action	comment	image
	4.b	<i>Simulate oral model performance</i>	1. Use new permeability value (PI) form drop-down	
Steps up and until here are filed in Handson II-Absorption_3.pksim5	4.b	<i>Simulate oral model performance</i>	Exclude absorption from colon ascendens –rectum e.g. by setting intestinal solubility (visible in “Advanced” view-mode) to 0 in these compartments	

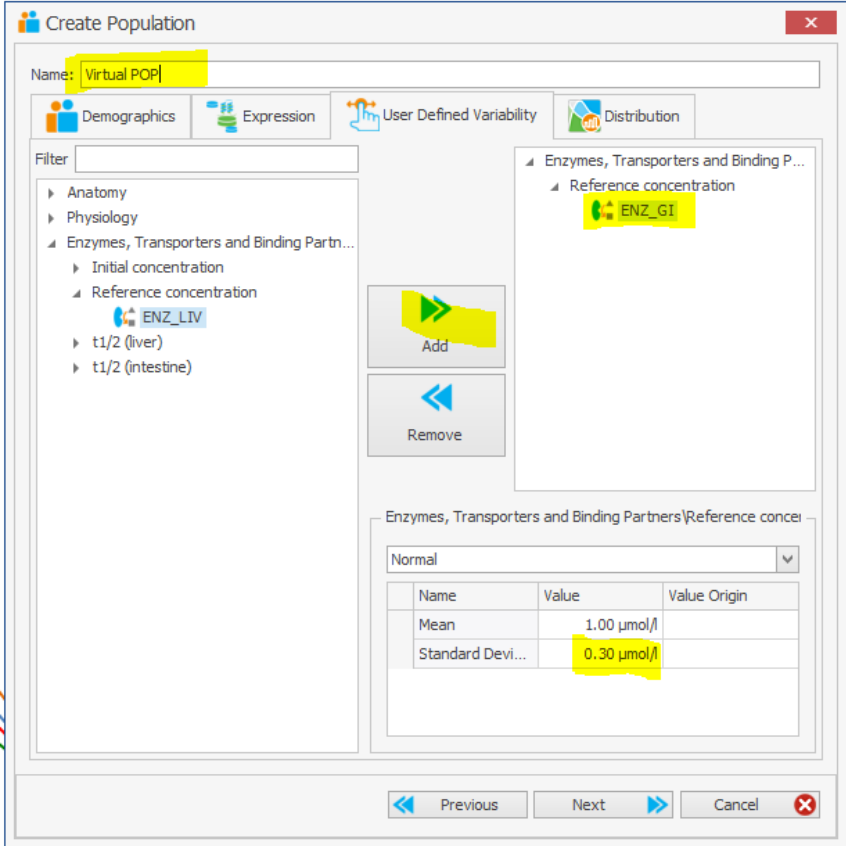
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	5a	<i>Parameter Identification</i>	Create a parameter Identification and include "ORAL_100mg"	
	5a	<i>Parameter Identification</i>	Delete IV data	

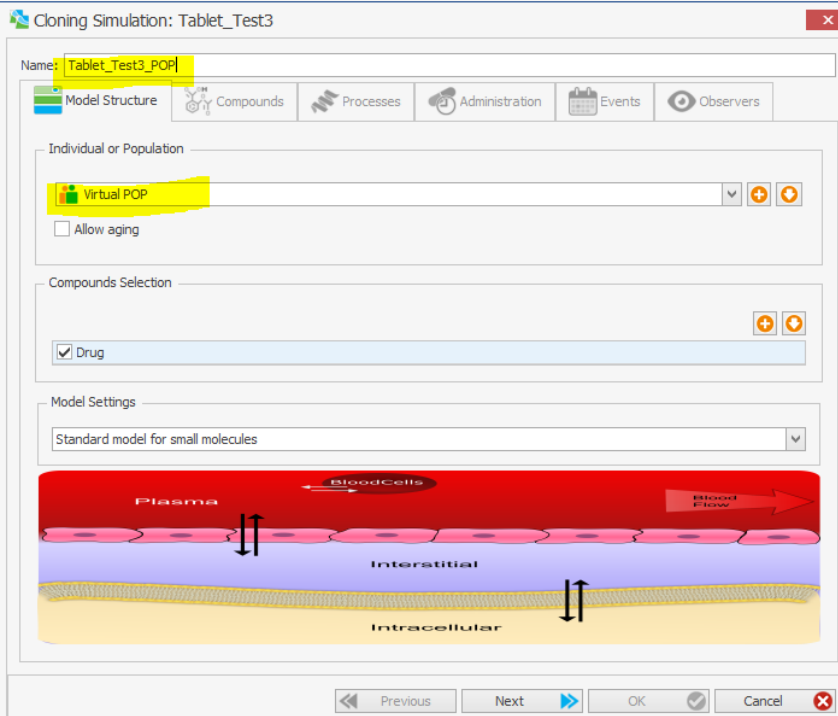
File	Step	action	comment	image
	5a	Parameter Identification	Select “Specific intestinal permeability (transcellular)” and “CLspec/[Enzyme]” for (only!) ENZ_GI and Run	
	5b	Transfer Parameter Identification	Transfer to Simulations from “Results” and “Commit to building block”	

File	Step	action	comment	image
Steps up and until now are saved in Handson II-Absorption_4.pksim5	6.a	<i>Look at results</i>		
(2) Formulation performance in virtual populations				
	7.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
				
Steps up and until now are saved in Handson II-Absorption_5.pksim5	7.b	<i>Set up simulations for different formulations for typical individual</i>	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.	

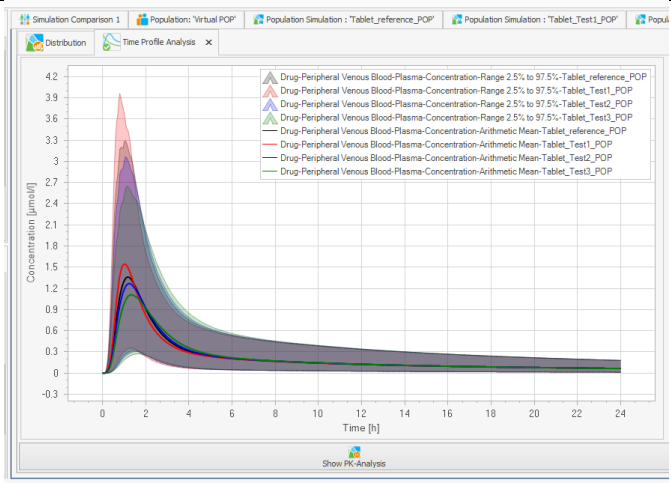
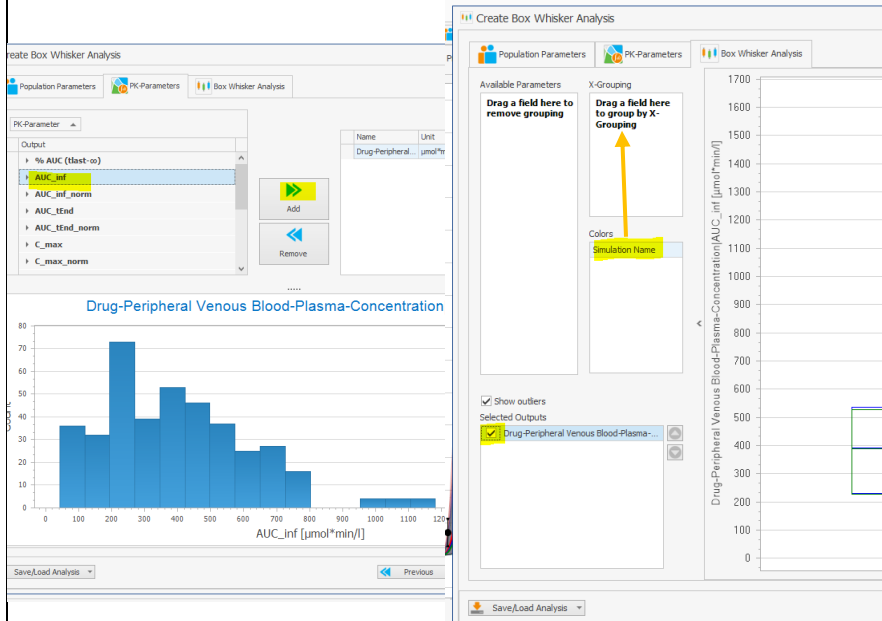
File	Step	action	comment	image
	8.a	Create a virtual population	Create virtual population based on "Man30", e.g., age 25-40 , 100% men, n=100	

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

File	Step	action	comment	image
	9	<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																																																				
	10	Run simulations	Run all formulations and add the 95% quantile and add AUC_inf and C_max for PK-parameters check.	<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>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><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>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></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	
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	11.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.	<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><div>Time units: 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><div>Add</div><div>Remove</div></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 checked="" type="checkbox"/></td><td>Arithmetic Mean</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>Arithmetic Standard Deviation</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>Geometric Mean</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>Geometric Standard Deviation</td><td>Solid</td></tr><tr><td><input type="checkbox"/></td><td>Min</td><td>Solid</td></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></table></div></div><div><div>Save/Load Analysis</div><div>Previous</div><div>Next</div><div>Cancel</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><div>% AUC (tlast-∞)</div><div>AUC_inf</div><div>AUC_inf_norm</div><div>AUC_t_end</div><div>AUC_t_end_norm</div><div>C_max</div><div>C_max_norm</div></div></div><div><div>Add</div><div>Remove</div></div><div><div>Create Grouping</div><div><table><tr><th>Name</th><th>Unit</th></tr><tr><td>Drug-Peripheral Venous ...</td><td>µmol*min/l</td></tr><tr><td>Drug-Peripheral Venous ...</td><td>µmol/l</td></tr></table></div></div><div><div>Drug-Peripheral Venous Blood-Plasma-Concentration AUC_inf</div><div></div></div><div><div>Save/Load Analysis</div><div>Previous</div><div>Next</div><div>Cancel</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 checked="" type="checkbox"/>	Arithmetic Mean	Solid	<input type="checkbox"/>	Arithmetic Standard Deviation	Solid	<input type="checkbox"/>	Geometric Mean	Solid	<input type="checkbox"/>	Geometric Standard Deviation	Solid	<input type="checkbox"/>	Min	Solid	<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	Name	Unit	Drug-Peripheral Venous ...	µmol*min/l	Drug-Peripheral Venous ...	µmol/l
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File	Step	action	comment	image
	11.a	Visualize results	Time Profile comparison	
	11.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	11.b	<i>Visualize results</i>	Repeat for C_max	