

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

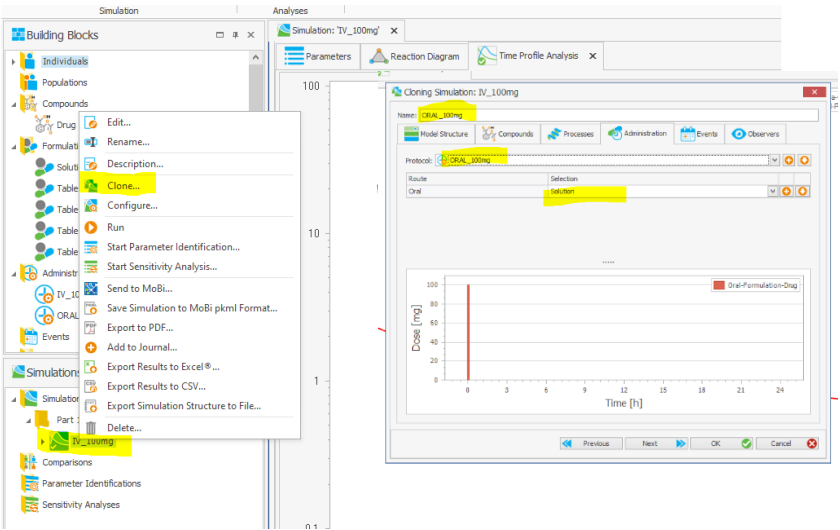
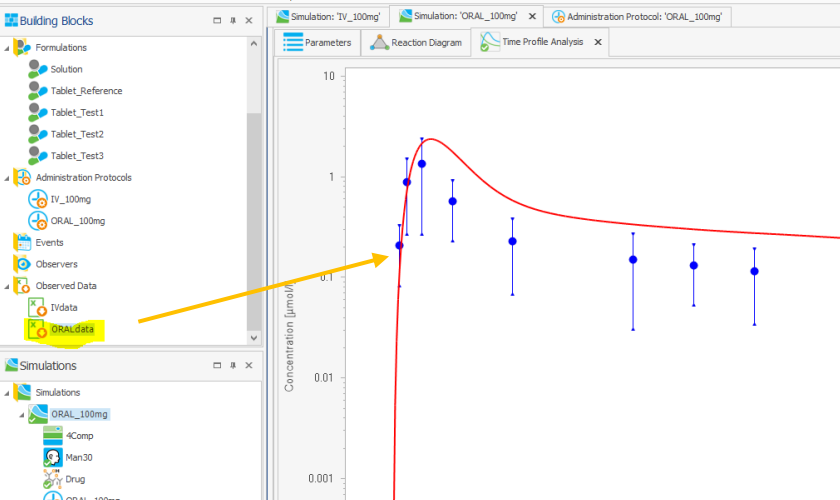
In this walkthrough guide basic operations and usage of PK-Sim are not show explicitly as there are excellent YouTube videos from scientist of [Clinical Pharmacy Saarland University](#) and detailed documentations on [Open Systems Pharmacology](#)

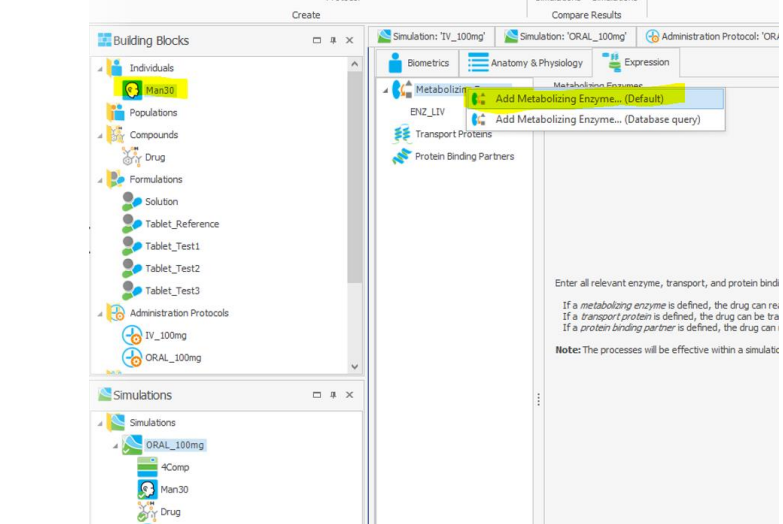
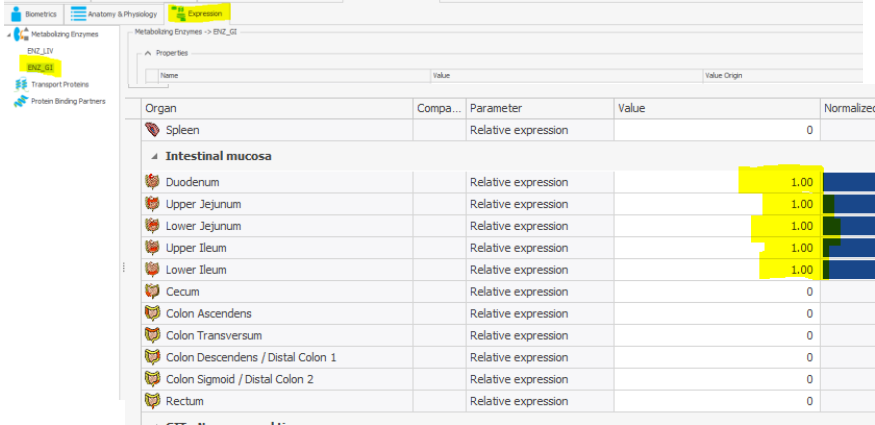
In this content overview links are pointing to these YouTube videos.

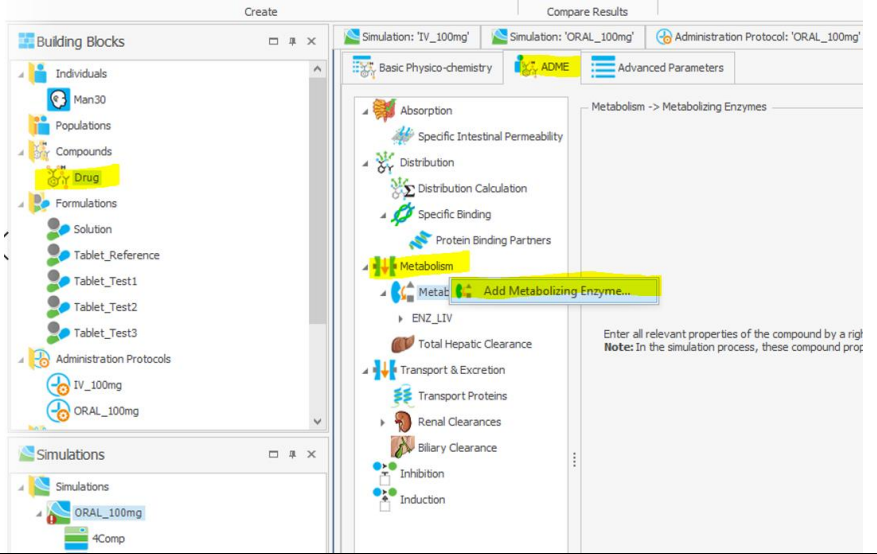
- Generate Healthy [individual](#)
- Generate [compounds](#) (from template DB)
- Set up [administration](#) scenarios
- Import [observed data](#)
- Build population and run [simulations](#) and compare to observed data
- Compare Simulations

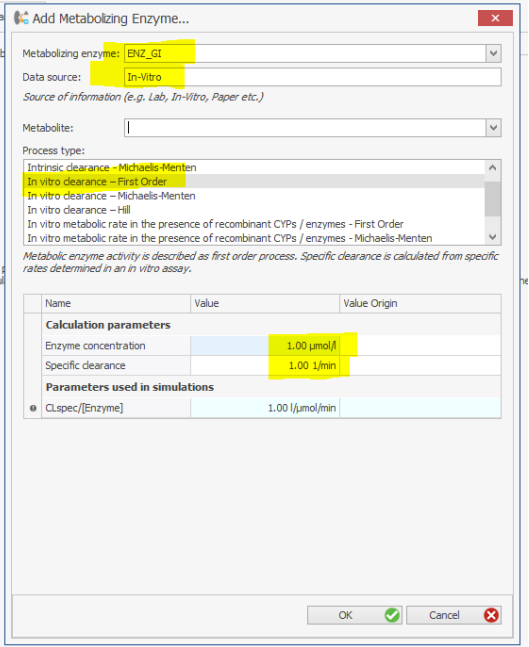
Detailed Step-by-Step

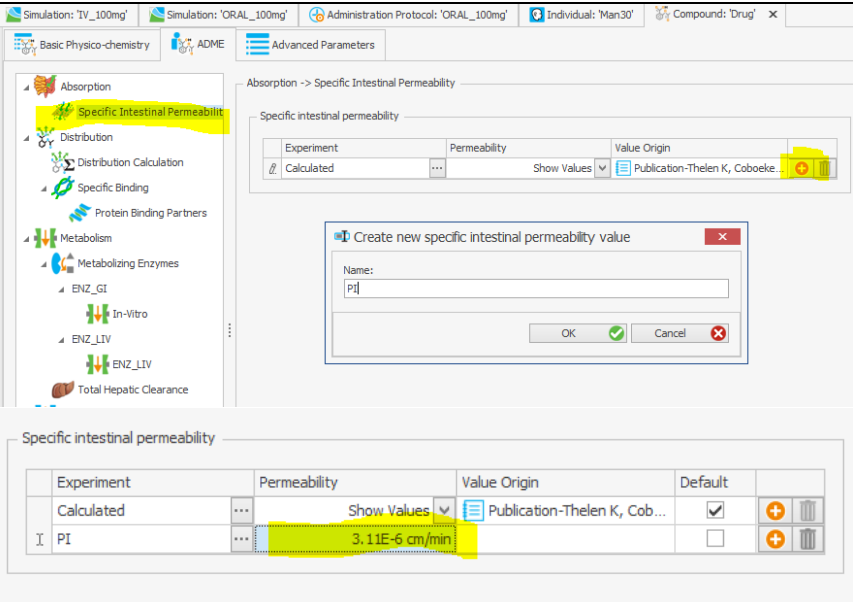
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
(1) Establish oral absorption model				

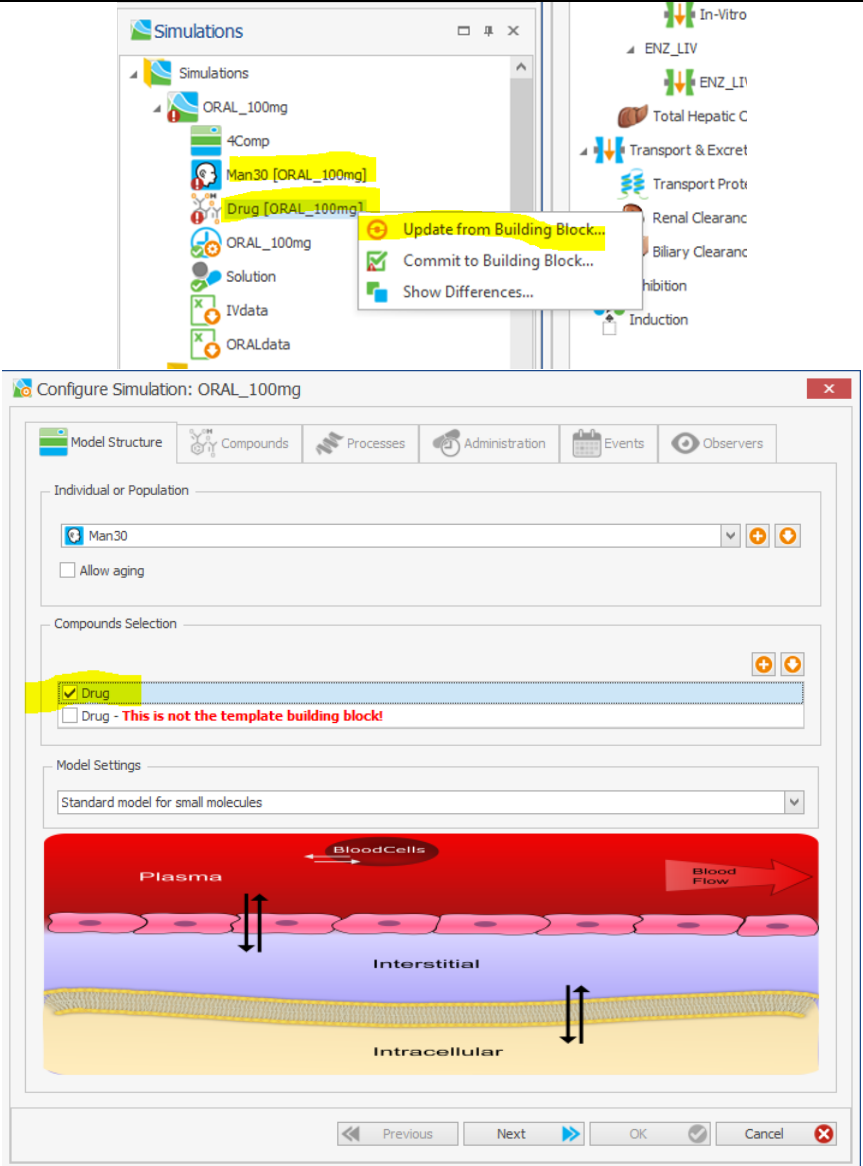
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	1.a	<i>Clone compound</i>	Clone simulation “IV_100mg”, name “ORAL_100mg” Select Administration protocol “ORAL_100mg” and formulation “Solution”	
	1.b	<i>Observe data</i>	Remove “IVdata” and add “ORALdata”	

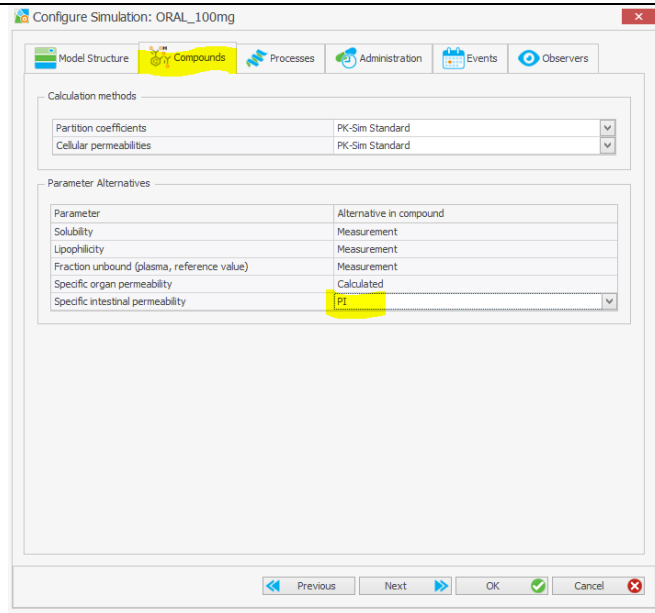
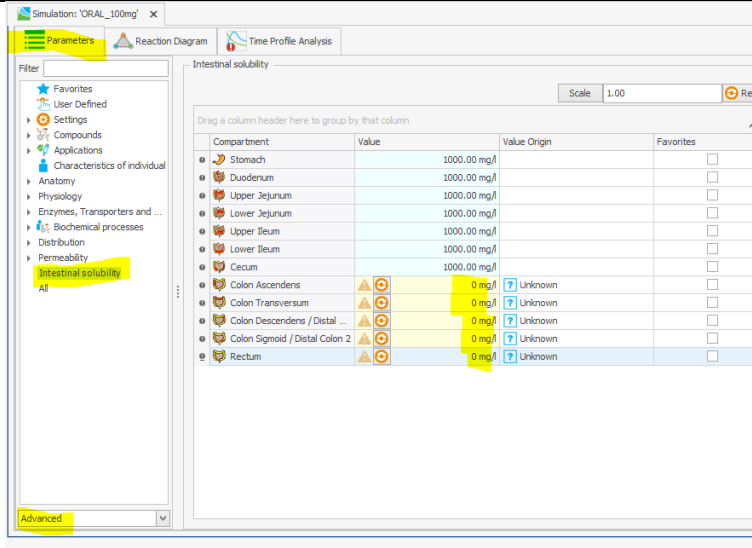
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image																																																																						
	2.a	Add GI enzyme in individual	Add “ENZ_GI” for individual Man30																																																																							
	2.a	Add GI enzyme in individual	Add relative expression = 1 in small intestine mucosa and keep other inputs as default	 <table border="1"> <thead> <tr> <th>Organ</th> <th>Compartment</th> <th>Parameter</th> <th>Value</th> <th>Normalized Value</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	Compartment	Parameter	Value	Normalized Value	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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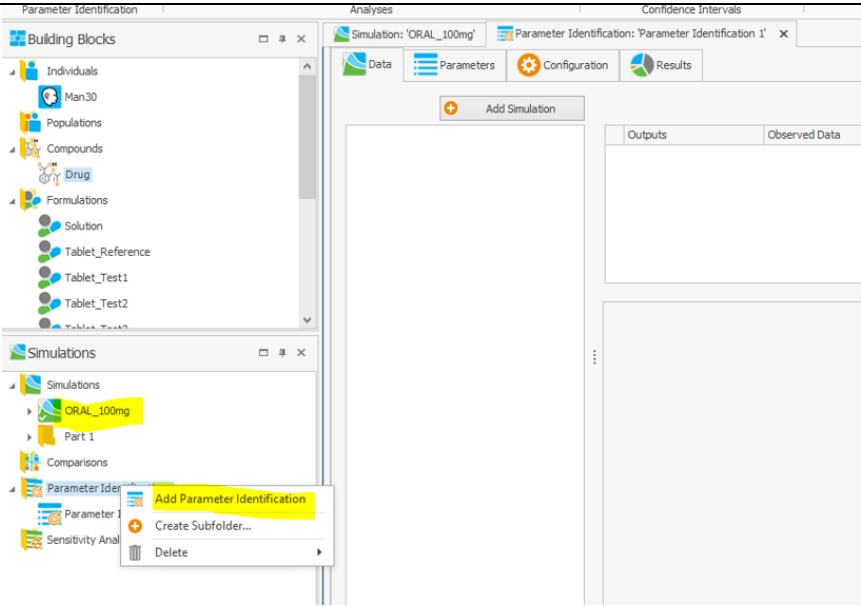
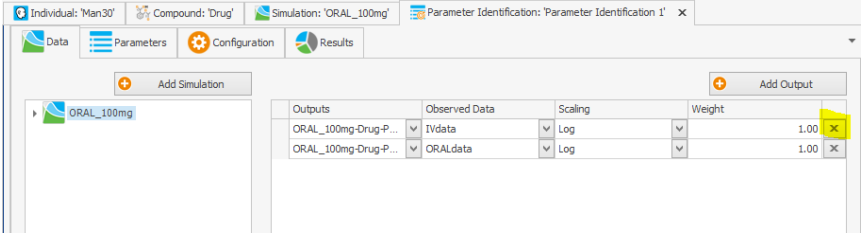
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	2.b	Add enzyme in compound	Add “Metabolizing enzyme” for ENZ_GI in compound Drug	

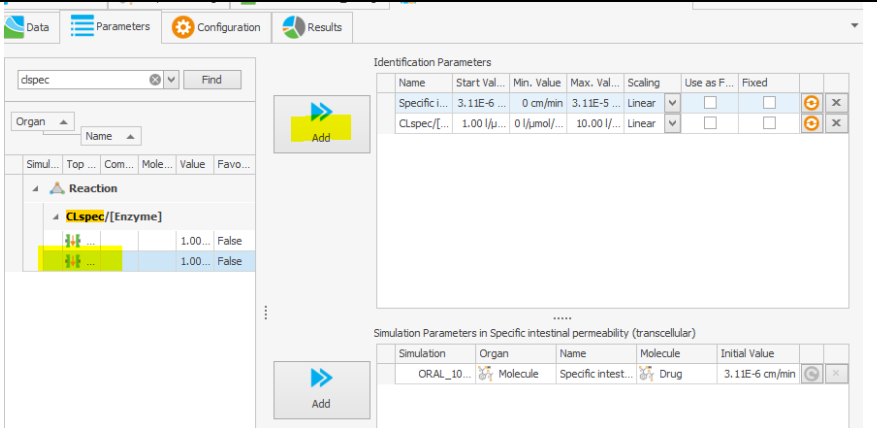
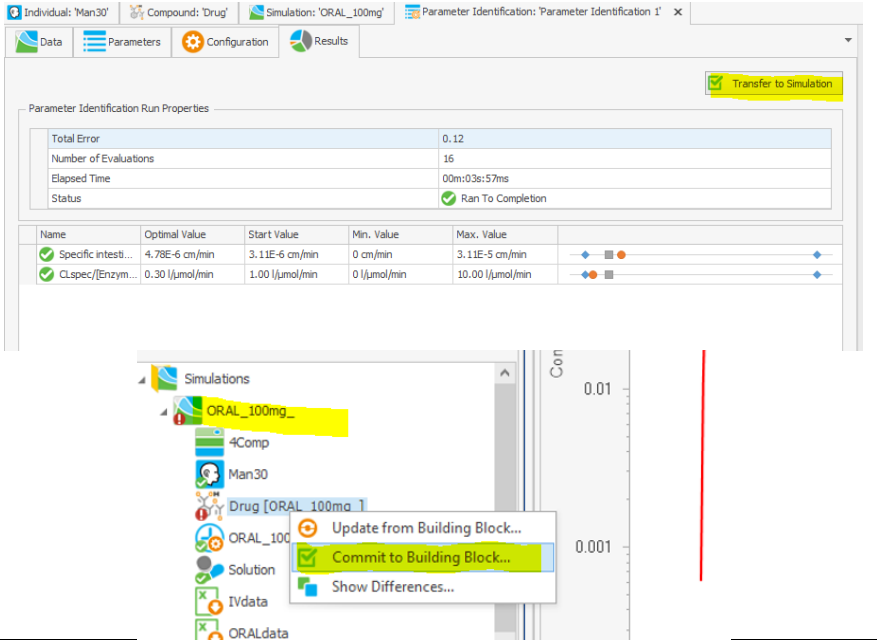
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	2.b	Add enzyme in compound	Fill in, ENZ_GI, in vitro, CL-first other, Enzyme concentration and specific clearance 1 μmol	

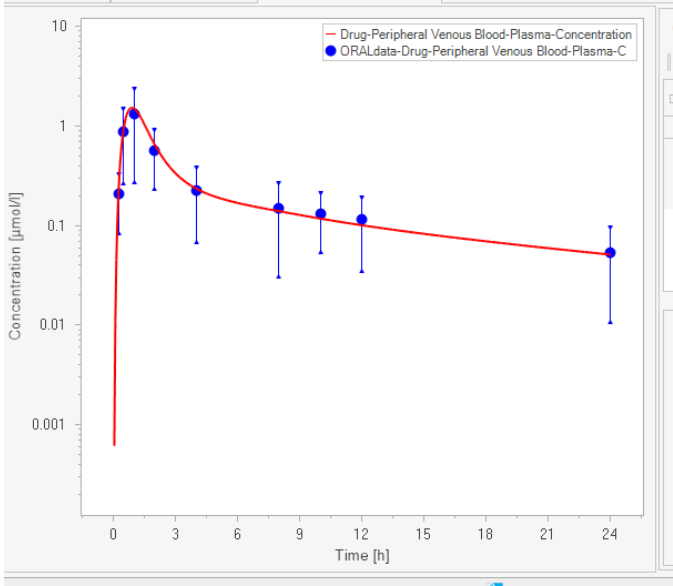
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image												
	2.b	Add enzyme in compound	Create new “specific intestinal permeability value” (PI) set to calculate value (3.11E-6 cm/min)	 <p>The screenshot displays the 'Specific Intestinal Permeability' configuration window. On the left, a tree view shows the 'Metabolizing Enzymes' section expanded, with 'ENZ_GI' and 'ENZ_LIV' visible. The main panel shows a table for 'Specific intestinal permeability' with columns for 'Experiment', 'Permeability', 'Value Origin', and 'Default'. A dialog box titled 'Create new specific intestinal permeability value' is open, with 'Name' set to 'PI'. Below the dialog, the main table shows a row for 'PI' with a value of '3.11E-6 cm/min' highlighted in yellow.</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>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	PI	...	3.11E-6 cm/min	
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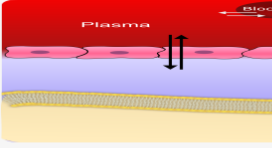
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	3.a	<i>Simulate oral model performance</i>	Update “Man30” and “Drug” from Building Block and Select the “Drug” in automatically opened configuration window	

File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	3.b	<i>Simulate oral model performance</i>	1. Use new permeability value (PI) form drop-down	
	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	

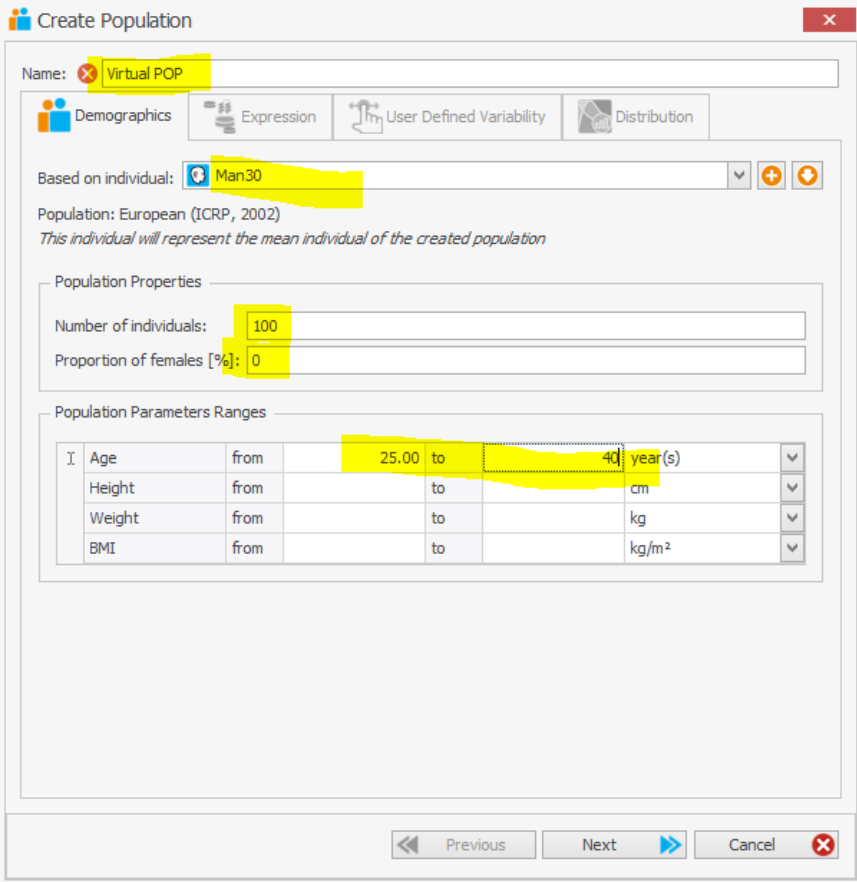
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	4a	Parameter Identification	Create a parameter Identification and include "ORAL_100mg"	
	4a	Parameter Identification	Delete IV data	

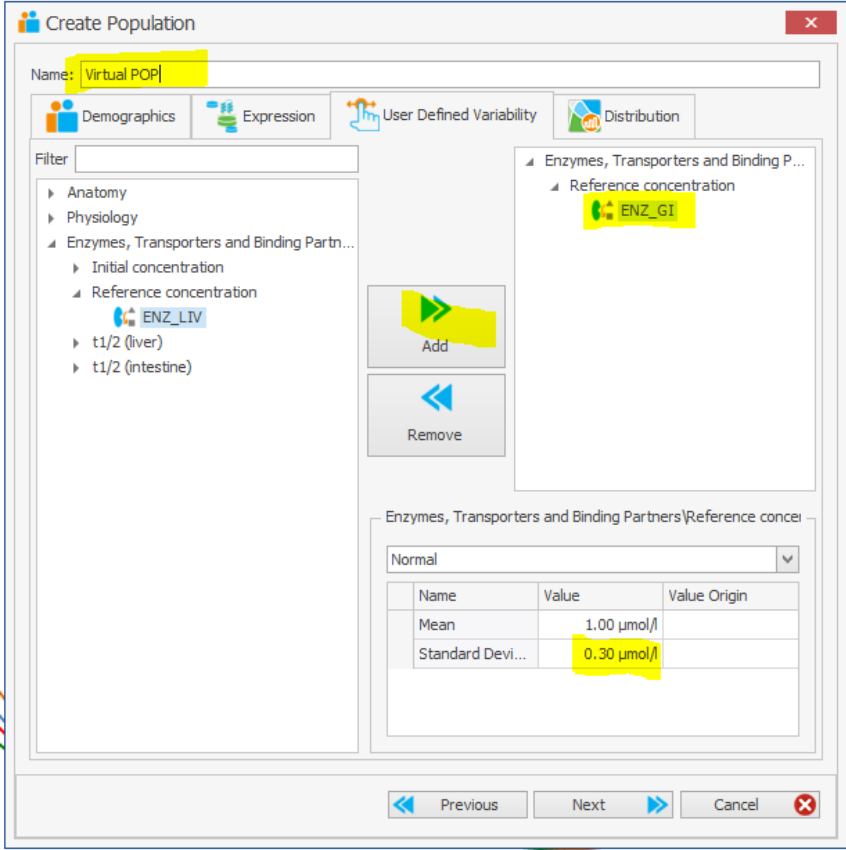
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	4a	<i>Parameter Identification</i>	Select “Specific intestinal permeability (transcellular)” and “CLspec/[Enzyme]” for (only!) ENZ_GI and Run	
	4b	<i>Transfer Parameter Identification</i>	Transfer to Simulations from “Results” and “Commit to building block”	

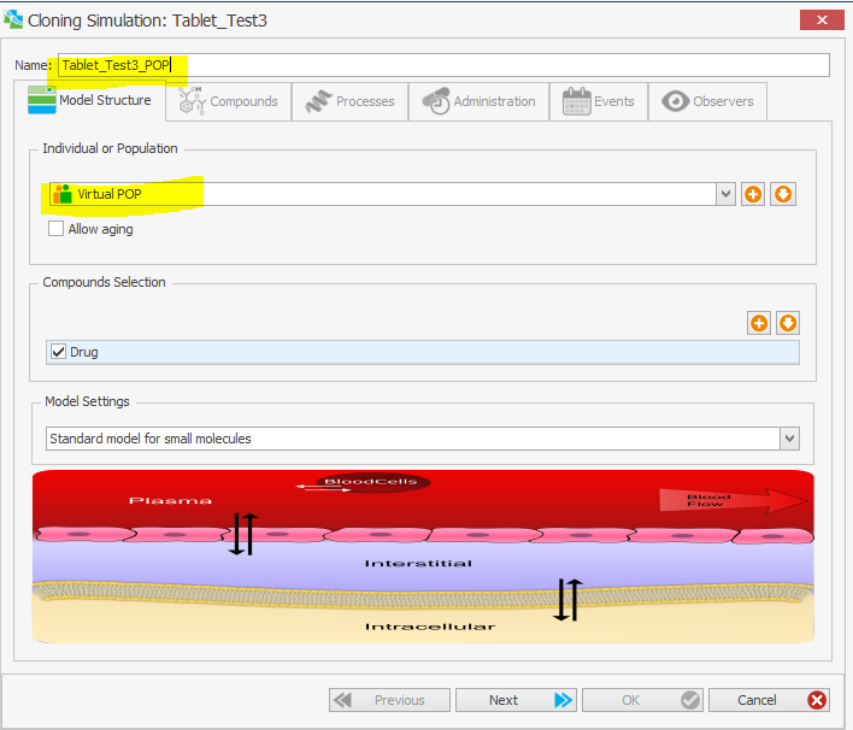
File (Session #2-HandsOn.pk sim5)	Step	action	comment	image
	5.a	<i>Look at results</i>		
(4) Formulation performance in virtual populations				
	6.a	<i>Set up simulations for different formulations for typical individual</i>	Clone simulation “ORAL_100mg” and name “Tablet_Reference” and select formulation “Tablet_Reference”. Remove ORALdata observations.	

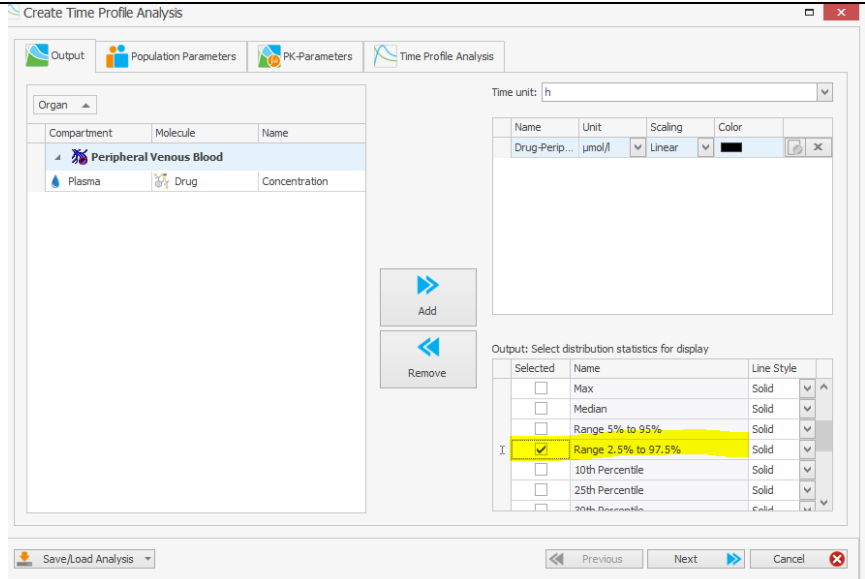
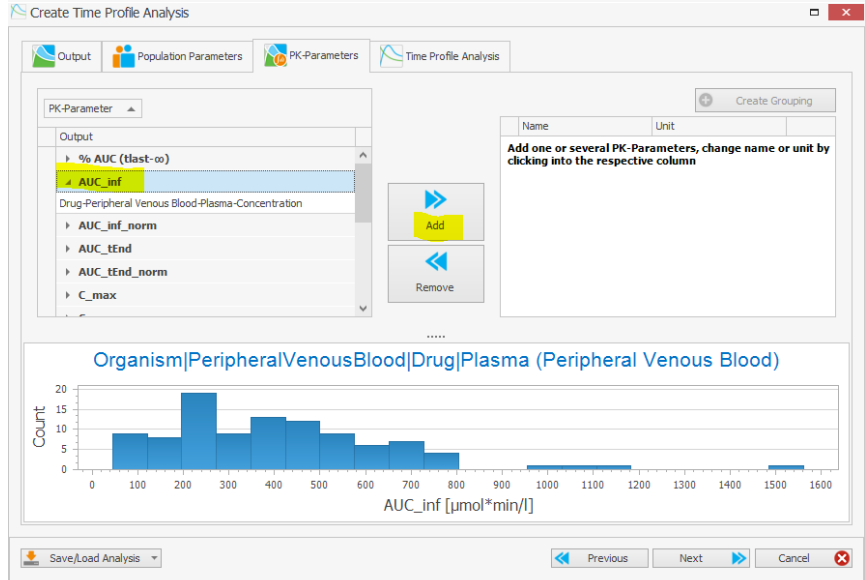
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
				<div><div><div><div>Cloning Simulation: ORAL_100mg</div><div><div>Name: Tablet_reference</div><div><div>Model Structure</div><div>Compounds</div><div>Processes</div><div>Administration</div><div>Events</div><div>Observers</div></div></div><div>Individual or Population</div><div><div>Man30</div><div><input type="checkbox"/> Allow aging</div></div><div>Compounds Selection</div><div><input checked="" type="checkbox"/> Drug</div><div>Model Settings</div><div>Standard model for small molecules</div><div></div></div></div><div><div>Cloning Simulation: ORAL_100mg</div><div><div>Name: Tablet_reference</div><div><div>Model Structure</div><div>Compounds</div><div>Processes</div><div>Administration</div><div>Events</div><div>Observers</div></div></div><div>Protocol: ORAL_100mg</div><div><div>Route</div><div>Oral</div><div><div>Selection</div><div>Tablet_Reference</div></div></div><div><div>Dose [mg]</div><div>100</div><div>80</div><div>60</div><div>40</div><div>20</div><div>0</div></div><div><div>Time [h]</div><div>0</div><div>3</div><div>6</div><div>9</div><div>12</div><div>15</div><div>18</div><div>21</div><div>24</div></div><div><div>Oral-Formulation-Drug</div></div><div><div>Previous</div><div>Next</div><div>OK</div><div>Cancel</div></div></div></div>

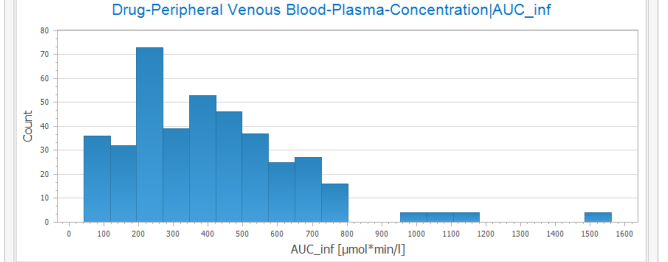
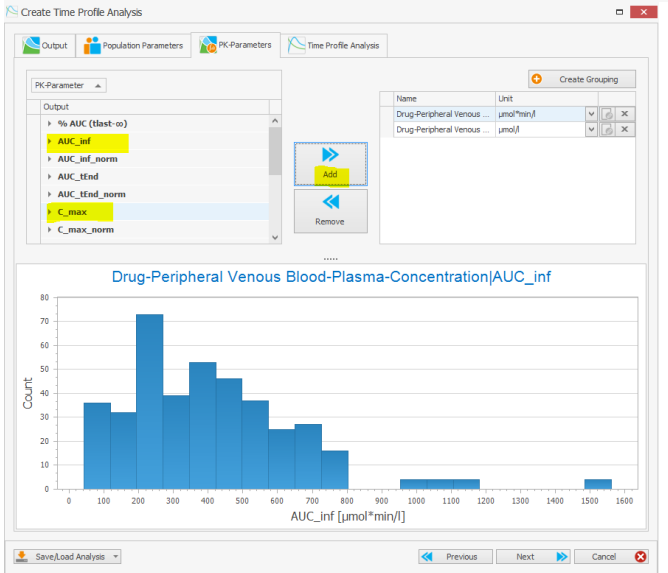
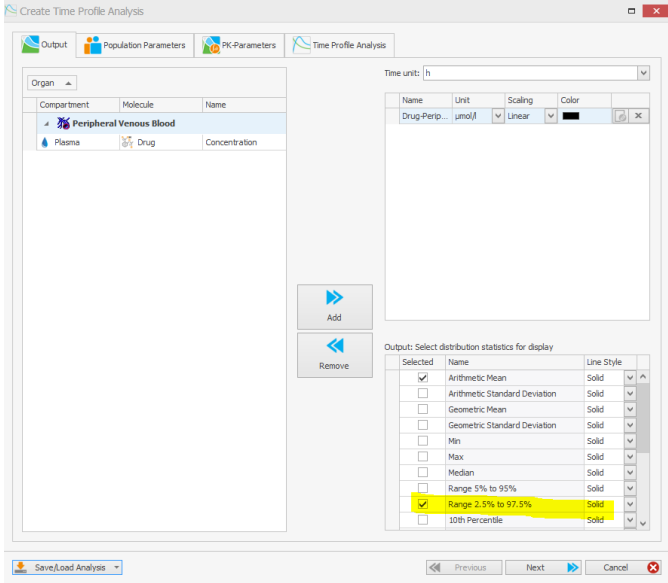
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	6.b	<i>Set up simulations for different formulations for typical individual</i>	Clone simulation “Tablet_Reference” to create simulations “Tablet_Test1”, “Tablet_Test2” and “Tablet_Test3” and run each simulation.	

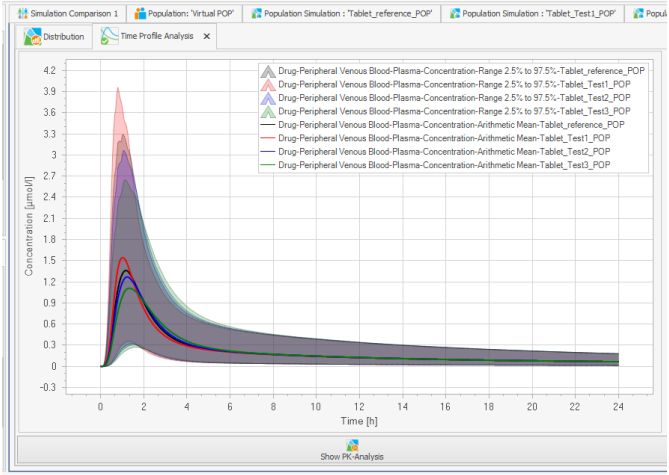
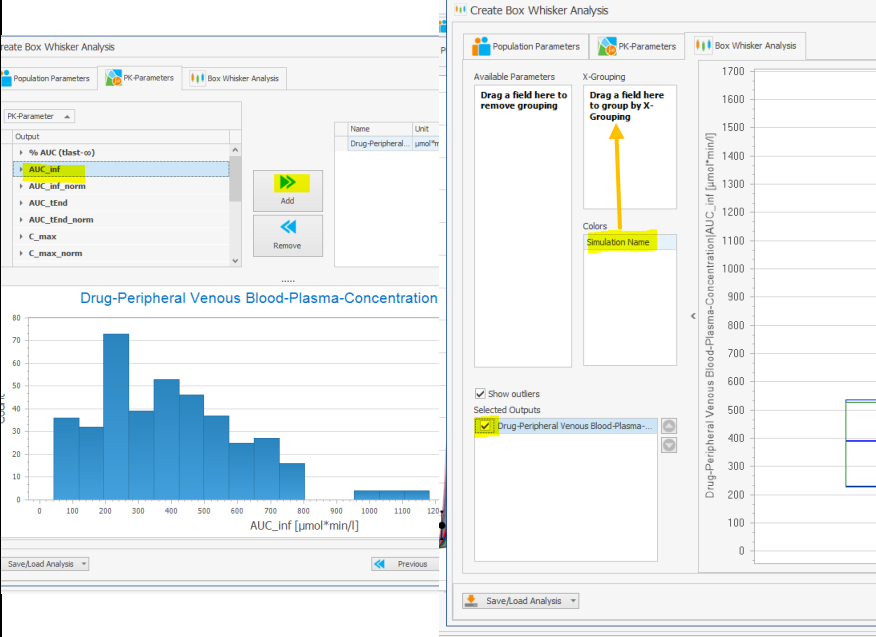
File (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	7.a	Create a virtual population	Create virtual population based on "Man30", e.g., age 25-40 , 100% men, n=100	

File (Session #2- HandsOn.pk sim5)	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 (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	8	Clone tablet simulations	Clone tablet simulations, add suffix “_POP”, and replace “Man30” with created virtual population for all tablet forms	

File (Session #2- HandsOn.pk sim5)	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><p>Create Time Profile Analysis</p><p>Organ: Peripheral Venous Blood</p><p>Output: Select distribution statistics for display</p><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>75th Percentile</td><td>Solid</td></tr></table><p>Buttons: Add, Remove, Save/Load Analysis, Previous, Next, Cancel</p></div> <div><p>Create Time Profile Analysis</p><p>PK-Parameter: AUC_inf</p><p>Output: % AUC (tlast-∞), AUC_inf, Drug-Peripheral Venous Blood-Plasma-Concentration, AUC_inf_norm, AUC_tEnd, AUC_tEnd_norm, C_max</p><p>Buttons: Add, Remove, Save/Load Analysis, Previous, Next, Cancel</p><p>Histogram: Organism PeripheralVenousBlood Drug Plasma (Peripheral Venous Blood)</p><p>Count vs AUC_inf [μmol*min/l]</p></div>	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"/>	75th Percentile	Solid
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	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.	<div></div>

File (Session #2-HandsOn.pk sim5)	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 (Session #2- HandsOn.pk sim5)	Step	action	comment	image
	10.b	Visualize results	Repeat for C_max	