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

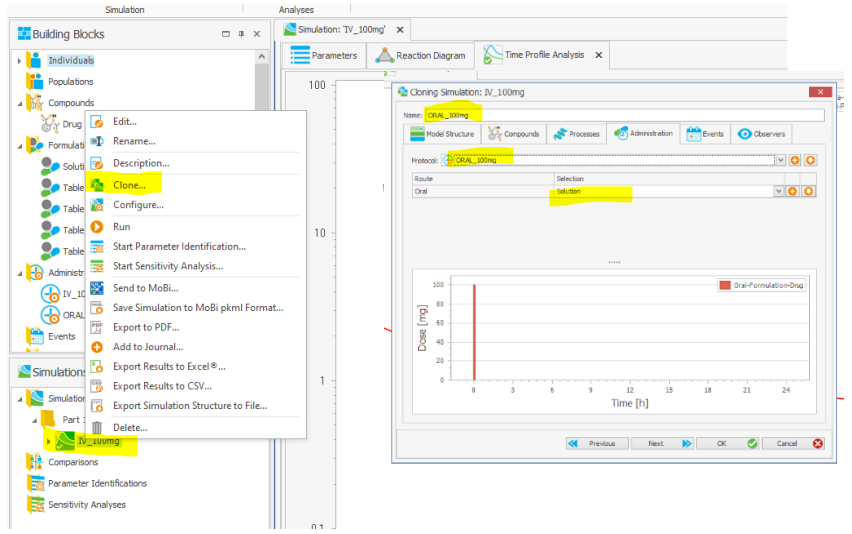
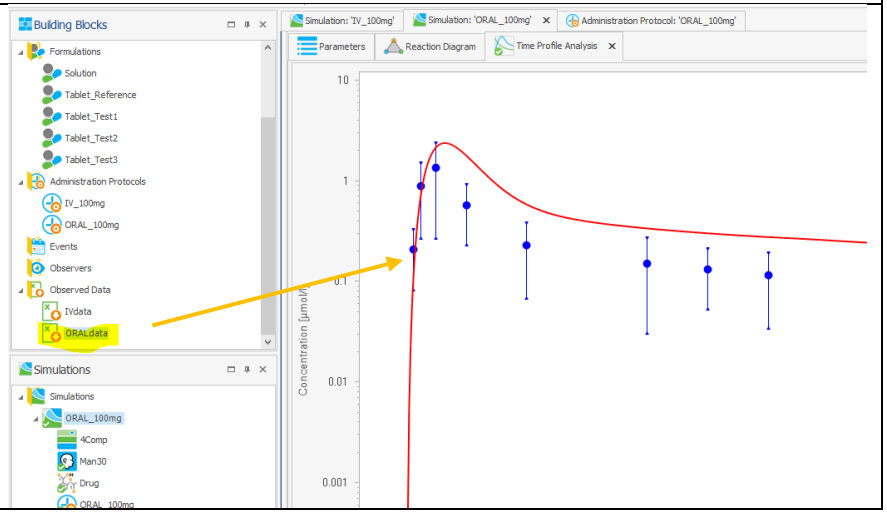
In this walkthrough guide basic operations and usage of PK-Sim are not show explicitly as there are excellent YouTube videos from scientist of Clinical Pharmacy Saarland University and detailed documentations on Open Systems Pharmacology

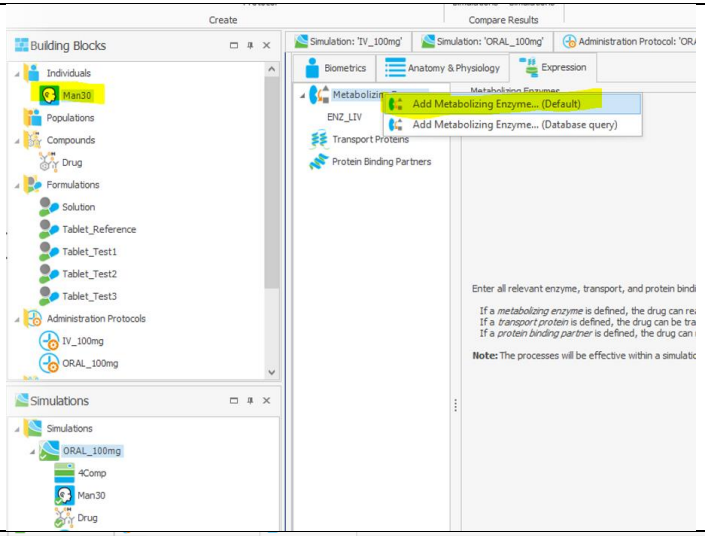
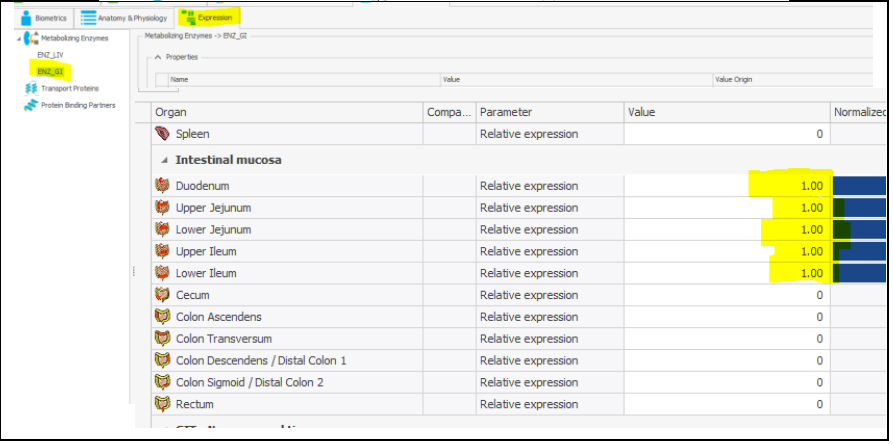
In this content overview links are pointing to these YouTube videos.

- 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

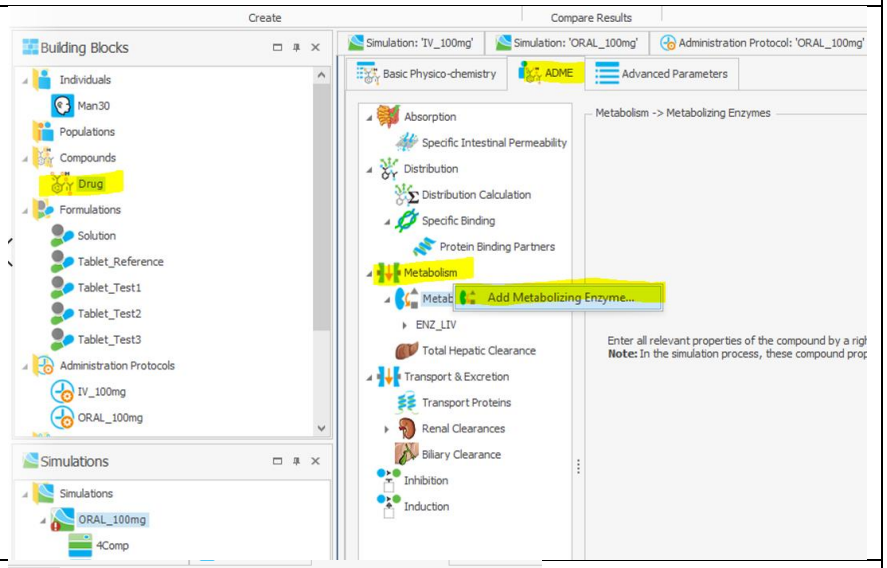
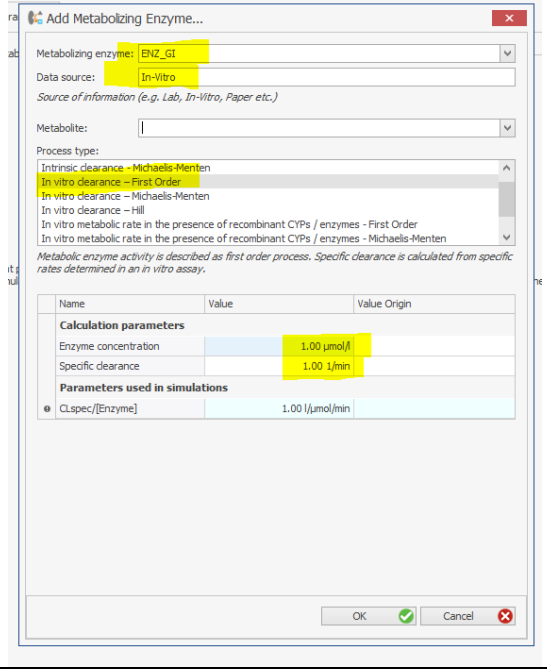
Detailed Step-by-Step

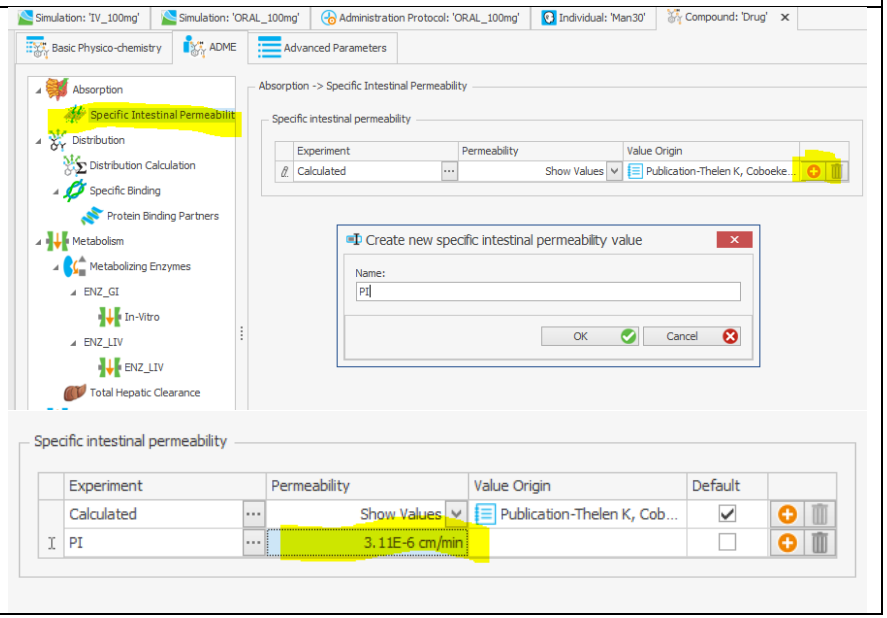
File	Step	action	comment	image
(1) Establish oral absorption model				

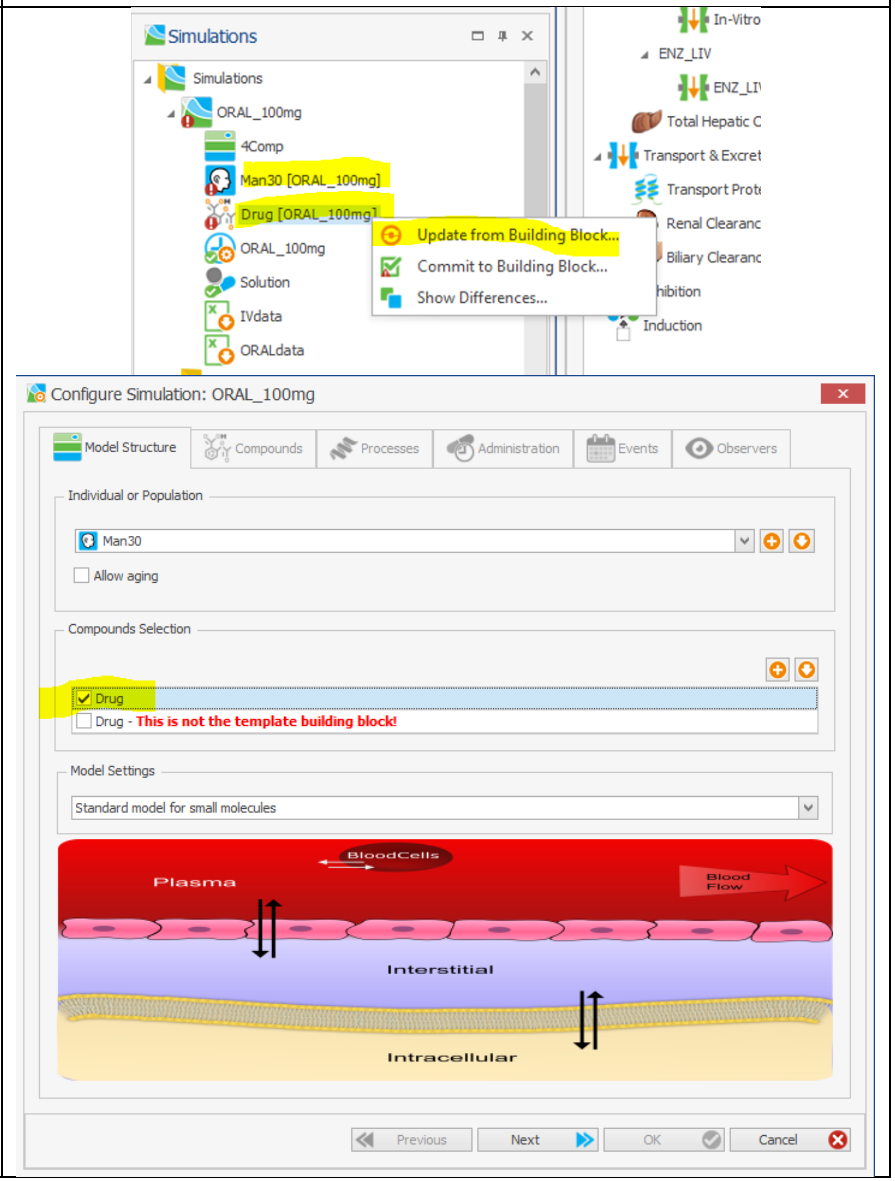
File	Step	action	comment	image
Handson II-Absorption_1	**1.a**	***Clone compound***	Clone simulation “IV_100mg”, name “ORAL_100mg” Select Administration protocol “ORAL_100mg” and formulation “Solution”. And run.	
	1.b	***Observe data***	Remove “IVdata” and add “ORALdata”	

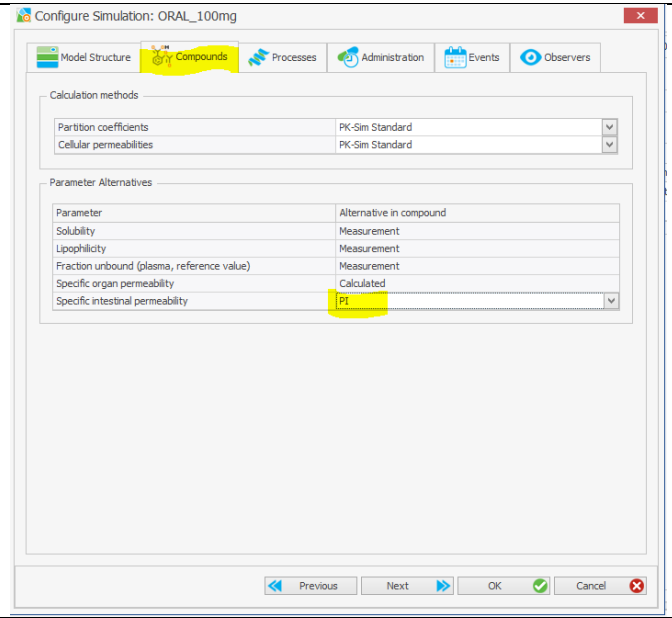
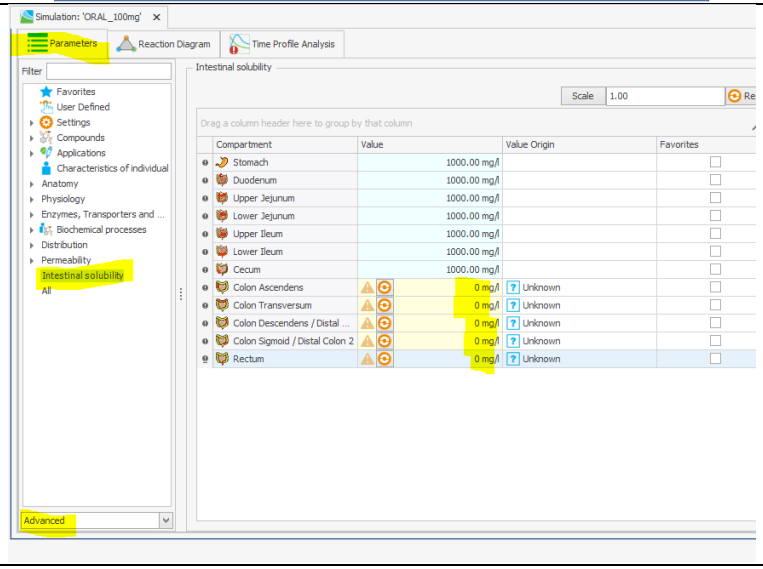
File	Step	action	comment	image
	2.a	***Add GI enzyme in individual***	Add "ENZ_GI" under Expression tab of individual Man30	
	2.a	***Add GI enzyme in individual***	Add relative expression = 1 in small intestine mucosa and keep other inputs as default	

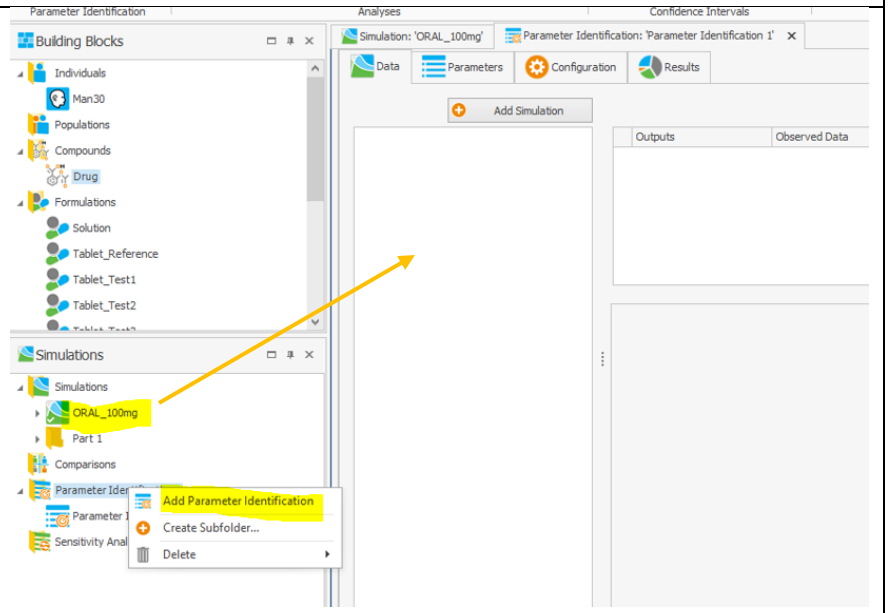
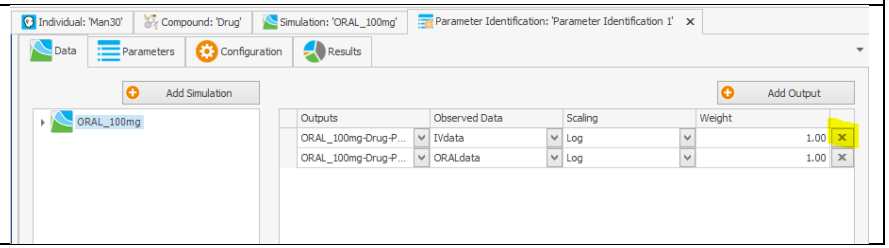
Organ	Compa...	Parameter	Value	Normalized
Spleen		Relative expression	0	
Intestinal mucosa				
Duodenum		Relative expression	1.00	
Upper Jejunum		Relative expression	1.00	
Lower Jejunum		Relative expression	1.00	
Upper Ileum		Relative expression	1.00	
Lower Ileum		Relative expression	1.00	
Cecum		Relative 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	

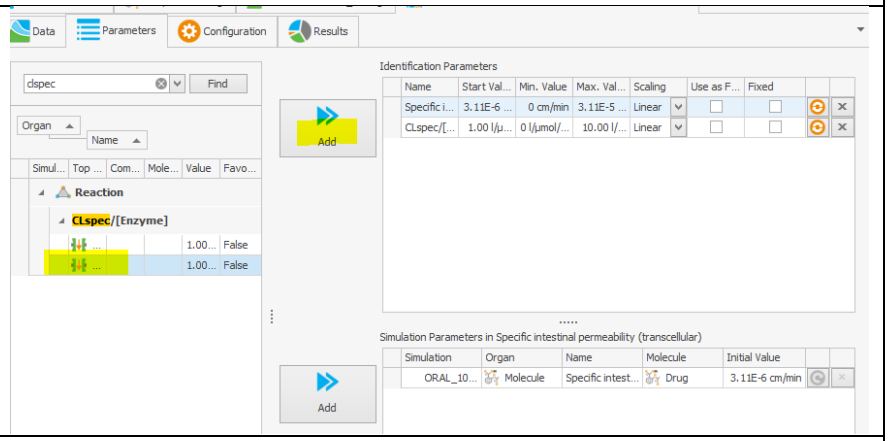
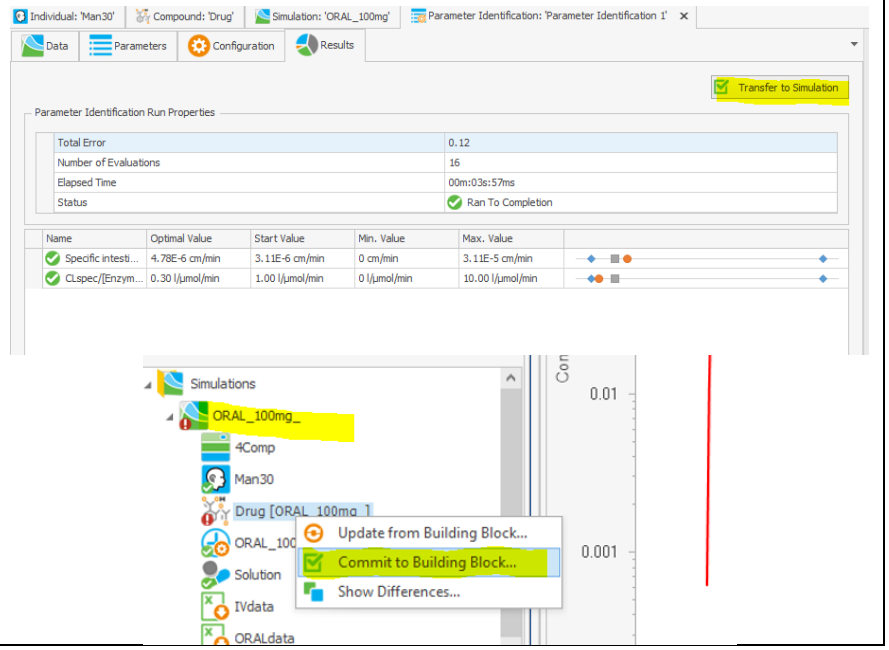
File	Step	action	comment	image
	2.b	***Add enzyme in compound***	Add “Metabolizing enzyme” for ENZ_GI in compound Drug under tab ADME	
	2.b	***Add enzyme in compound***	Fill in, ENZ_GI, in vitro, CL-first other, Enzyme concentration and specific clearance 1 µmol	

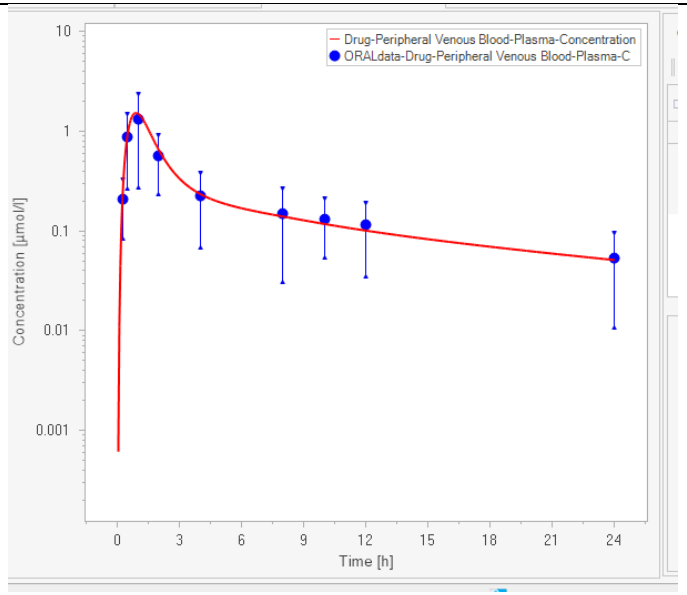
File	Step	action	comment	image
Steps up and until this point are given in Handson II-Absorption_2	**2.b**	***Add enzyme in compound***	Create new “specific intestinal permeability value” (PI) set to calculate value (3.11E-6 cm/min)	

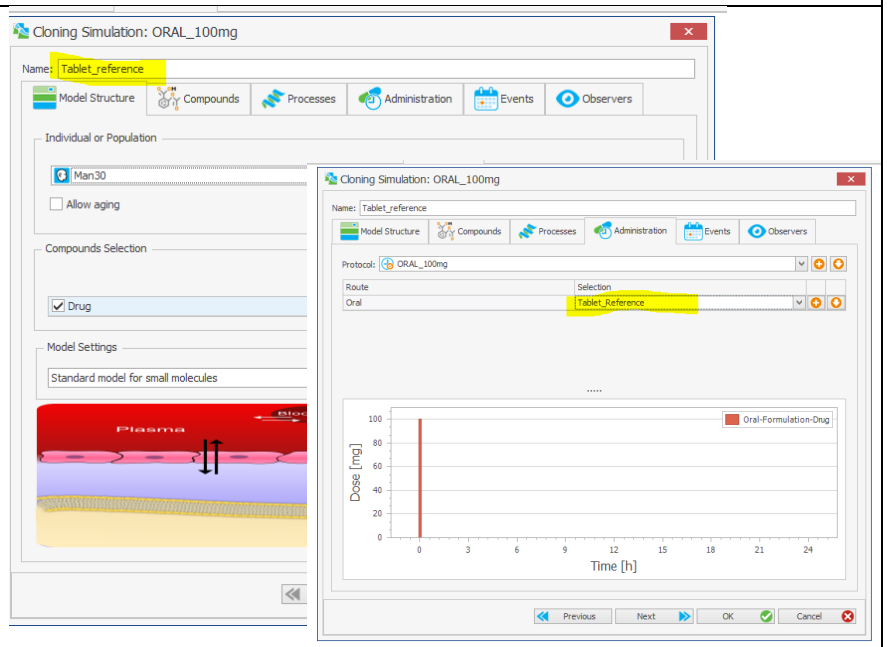
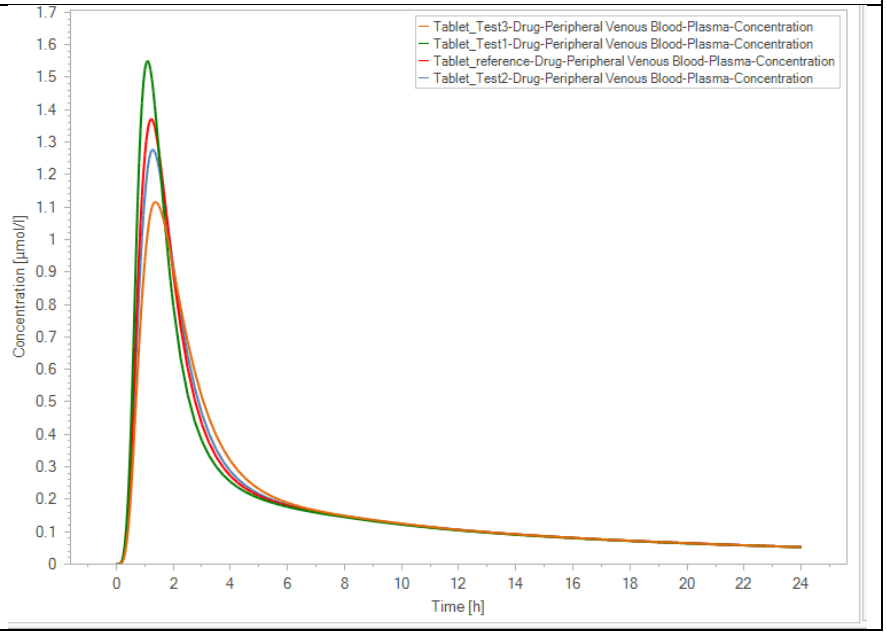
File	Step	action	comment	image
	3.a	***Simulate oral model performance***	Update “Man30” and “Drug” from Building Block and Select the “Drug” in automatically opened configuration window	

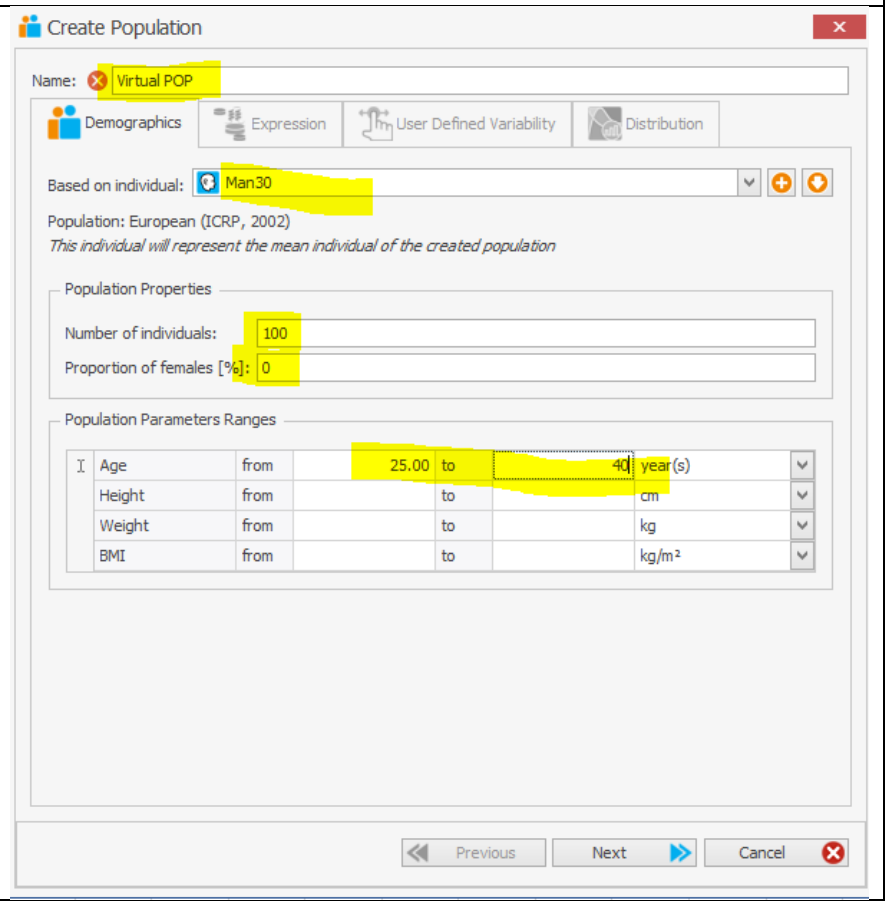
File	Step	action	comment	image
	3.b	***Simulate oral model performance***	1. Use new permeability value (PI) form drop-down	
Steps up and until here are filed in Handson II-Absorption_3 .pksim5	**3.b**	***Simulate oral model performance***	Exclude absorption from colon ascendens –rectum e.g. by setting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

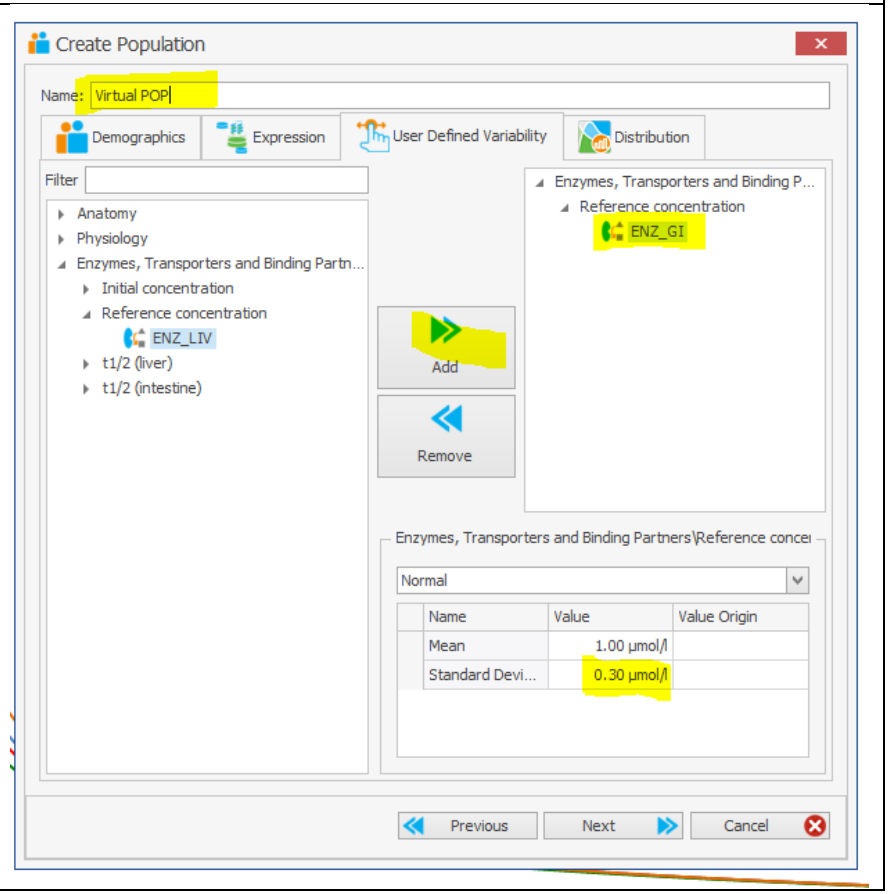
File	Step	action	comment	image
	4a	***Parameter Identification***	Create a parameter Identification and include “ORAL_100mg”	
	4a	***Parameter Identification***	Delete IV data	

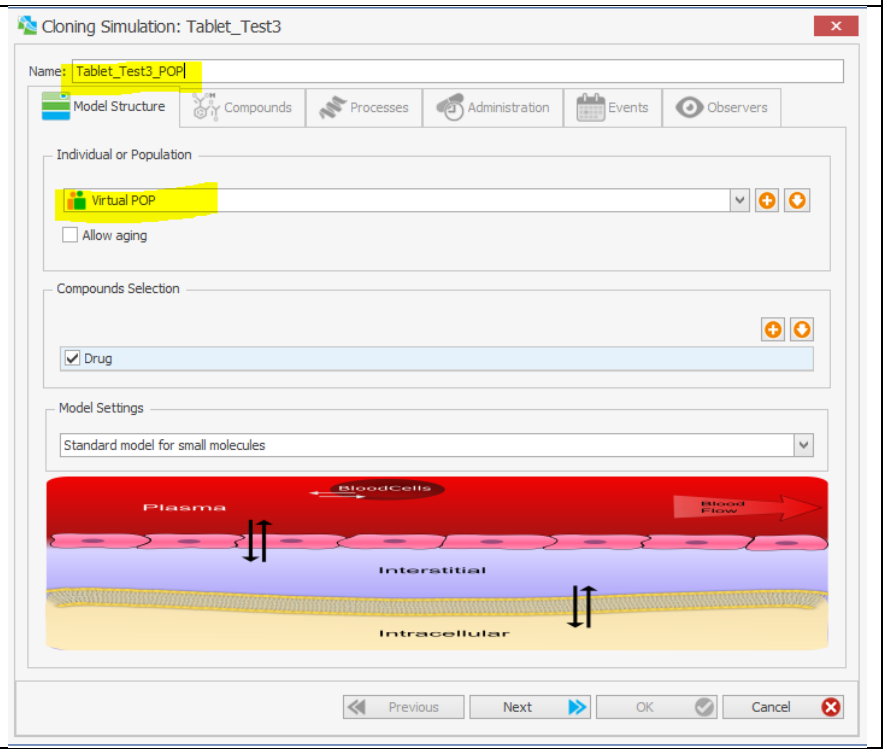
File	Step	action	comment	image
	4a	***Parameter Identification***	Select “Specific intestinal permeability (transcellular)” and “CLspec/[Enzyme]” for (only!) ENZ_GI and Run	
	4b	***Transfer Parameter Identification***	Transfer to Simulations from “Results” and “Commit to building block”	

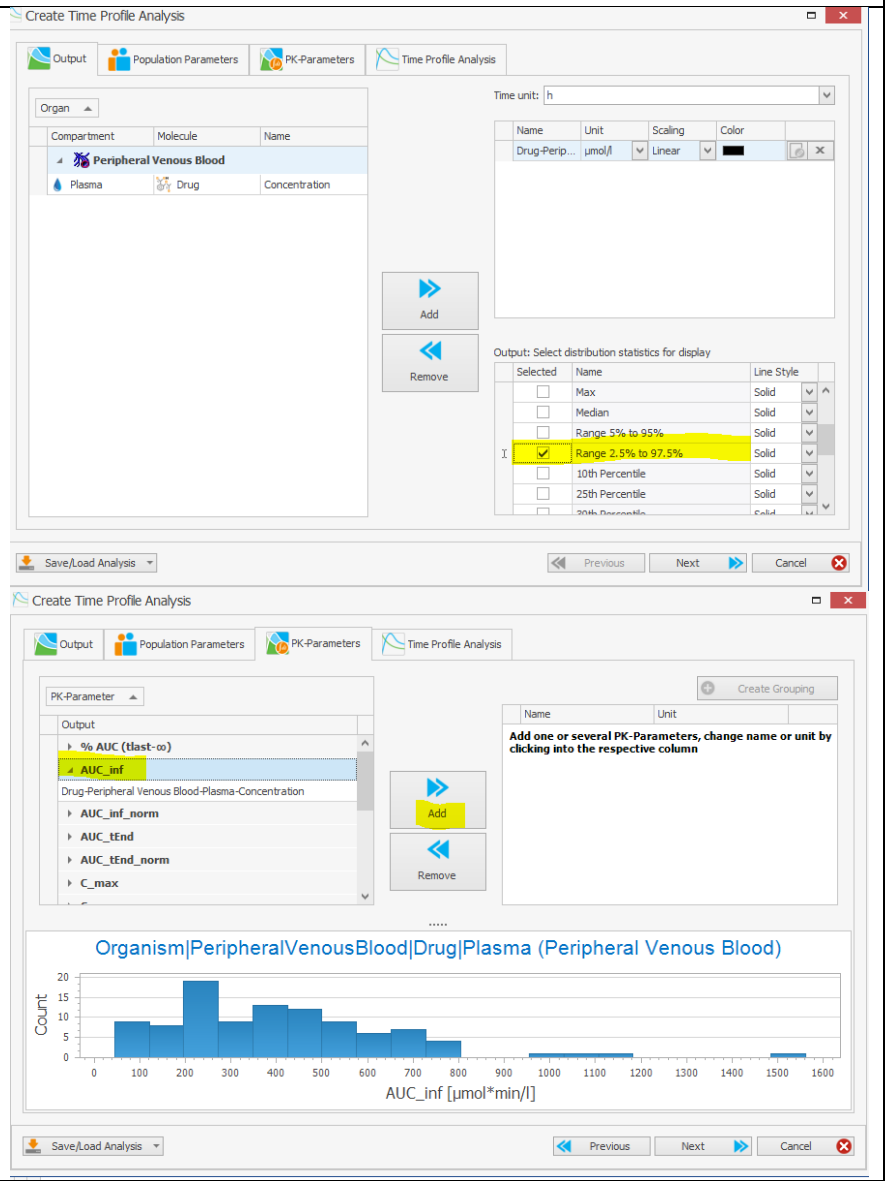
File	Step	action	comment	image
Steps up and until now are saved in Handson II-Absorption_4.pksim5	**5.a**	***Look at results***		
(4) Formulation performance in virtual populations				
	6.a	***Set up simulations for different formulations for typical individual***	Clone simulation "ORAL_100mg" and name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

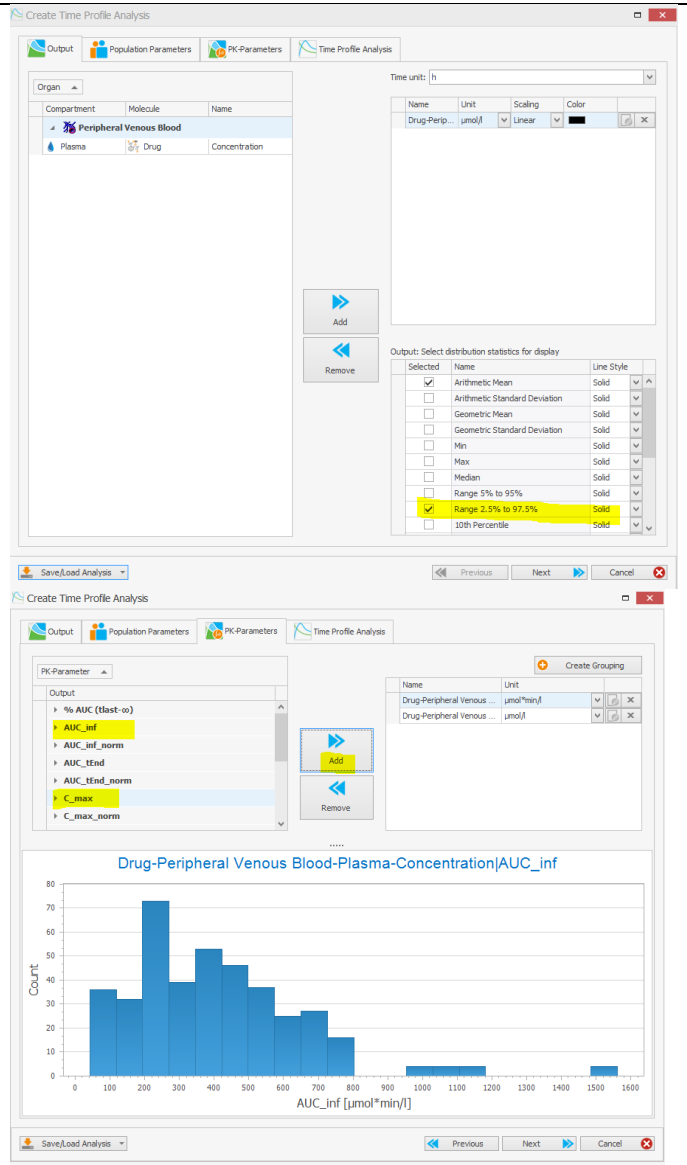
File	Step	action	comment	image
				
Steps up and until now are saved in Handson II-Absorption_5.pksim5	**6.b**	***Set up simulations for different formulations for typical individual***	Clone simulation "Tablet_Reference" to create simulations "Tablet_Test1", "Tablet_Test2" and "Tablet_Test3" and run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

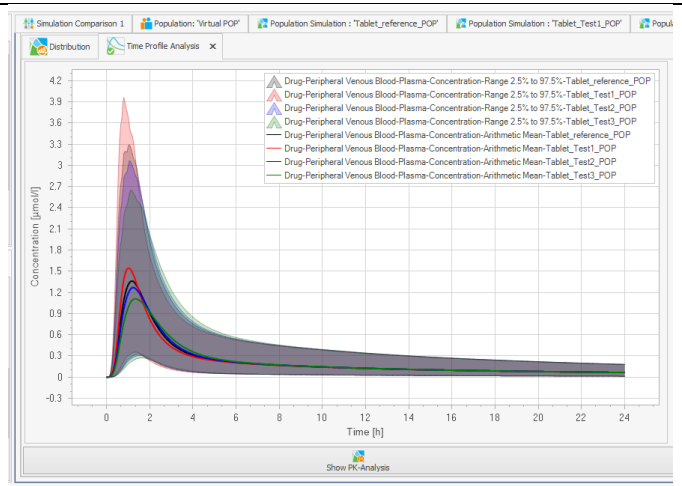
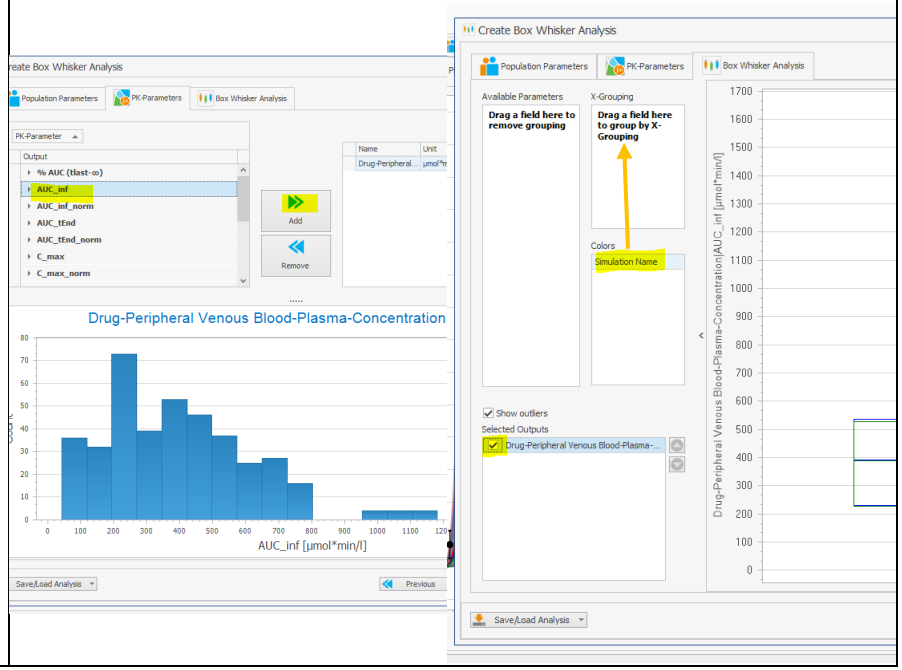
File	Step	action	comment	image
	7.a	***Create a virtual population***	Create virtual population based on ”Man30”, e.g., age 25-40 , 100% men, n=100	

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	***Clone tablet simulations***	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.	

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.	

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**	***Visualize results***	Repeat for C_max