Tools and workflows for automated reporting of PBPK modeling with OSP

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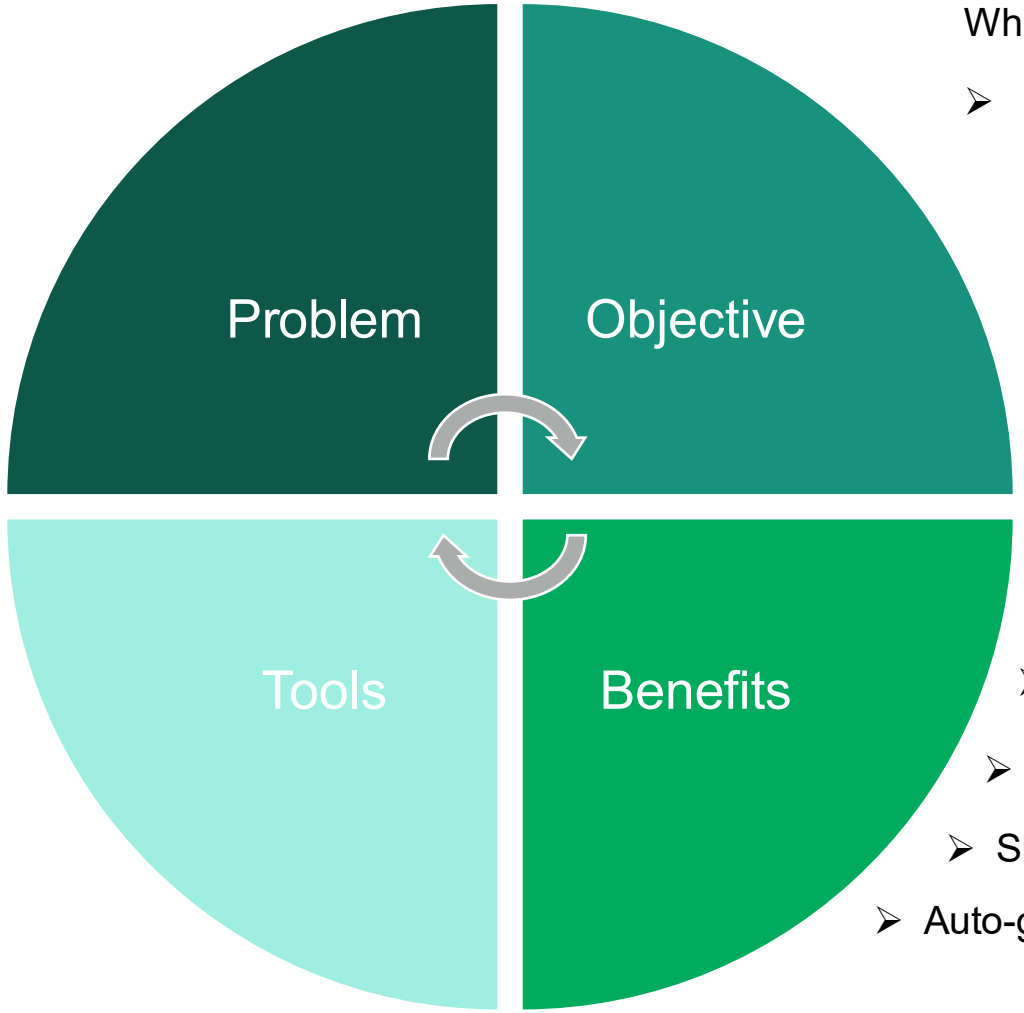
Life forward

PBPK Automated Reporting: Why, what and how

Why:

- Reporting PBPK analysis results is typically done **manually** by copying/inserting relevant tables and figures into a Word document or a LaTeX template.
- This process is inefficient, time-consuming, and prone to errors.



What:

- Within **Boehringer Ingelheim,** automation techniques were implemented to **enhance the efficiency** of PBPK report generation.

How:

- Rstudio & OSPS R packages
  - osp.snapshots package
  - ospsuite package

- Faster reporting
- Consistent quality
- Fewer manual errors
- Simplified QC process
- Auto-generated figures and tables

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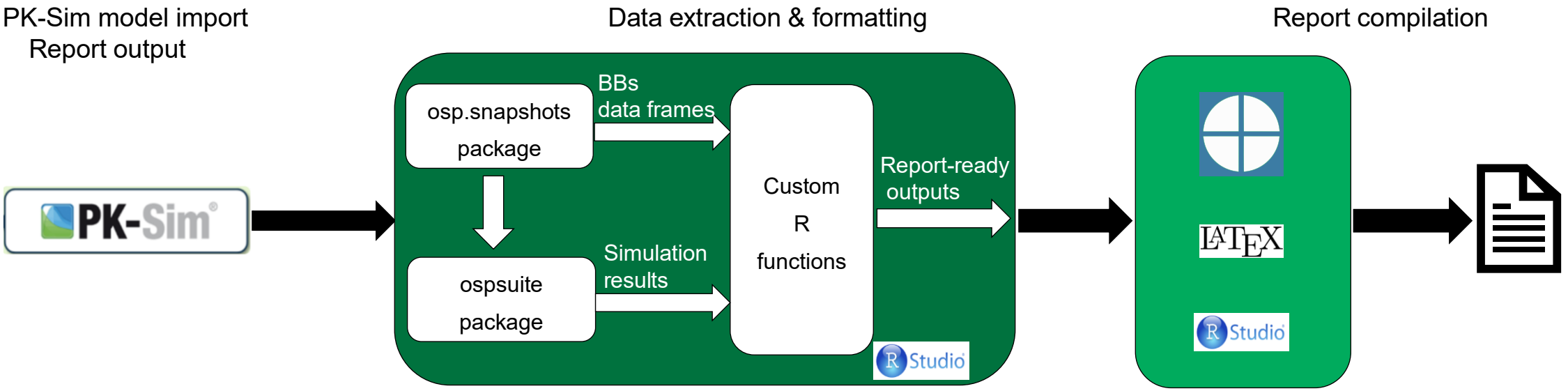
Automated PK-Sim®-Related Reporting Workflow at Boehringer Ingelheim



- Snapshot PK-Sim model

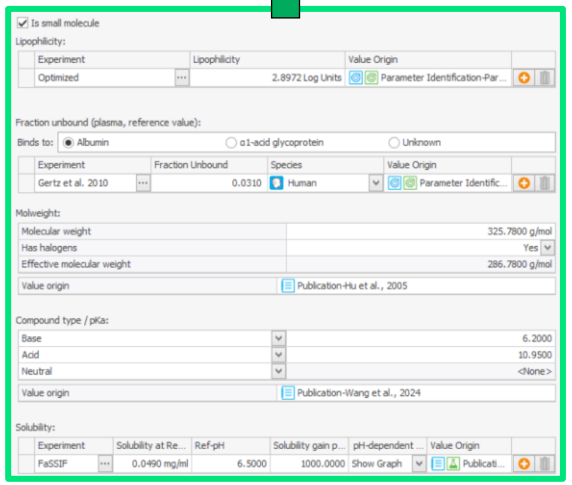
- **osp.snapshots:** extracts Building Blocks (BB) data as data frames
- **ospsuite:** computes simulation results
- **R functions**: presents extracted data as report-ready outputs

- **Quarto:** report sections
- **LaTeX:** report format & layout
- **RStudio:** report binder

osp.snapshots Package: from Compounds BB Input to Output

Input: snapshot data/nested object

```
"Compounds": [
  {
    "Name": "ExampleDrug",
    "IsSmallMolecule": true,
    "PlasmaProteinBindingPartner": "Albumin",
    "Lipophilicity": [...],
    "FractionUnbound": [...],
    "Solubility": [...],
    "IntestinalPermeability": [...],
     ...
  }
          ]
```



intermediate: osp.snapshots data frame

compound	category	type	parameter	value	unit	data_source	source
ExampleDrug	physicochemical_property	lipophilicity	Optimized	2.8972038771	Log Units	NA	Parameter optimization
ExampleDrug	physicochemical_property	fraction_unbound	Gertz et al. 2010	0.031	NA	NA	Parameter optimization
ExampleDrug	physicochemical_property	molecular_weight	NA	325.78	g/mol	NA	Hu et al., 2005
ExampleDrug	physicochemical_property	halogens	Cl	1	NA	NA	Hu et al., 2005
ExampleDrug	physicochemical_property	halogens	F	1	NA	NA	Hu et al., 2005
ExampleDrug	physicochemical_property	pKa	base	6.2			
ExampleDrug	physicochemical_property	pKa	acid	10			
ExampleDrug	physicochemical_property	solubility	pH 6.5	0.0			
ExampleDrug	physicochemical_property	intestinal_permeability	Optimized	0.0			
ExampleDrug	protein_binding_partners	SpecificBinding	koff, GABRG2	1			
ExampleDrug	protein_binding_partners	SpecificBinding	Kd, GABRG2	1.8			
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	Km, CYP3A4	4			
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	kcat, CYP3A4	8.7			
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	Km, UGT1A4	37			
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	kcat, UGT1A4	4.7			
ExampleDrug	renal_clearance	GlomerularFiltration	GFR fraction	0.6			

Output:

customized table

Parameter	Value	Unit	Source
Lipophilicity	2.897	Log Units	Parameter optimization
Fu-plasma	0.031	-	Parameter optimization
Molecular Weight	325.8	g/mol	Hu et al., 2005
Halogens, Cl	1	-	Hu et al., 2005
Halogens, F	1	-	Hu et al., 2005
pKa, base	6.2	-	Wang et al., 2024
pKa, acid	10.95	-	Wang et al., 2024
Solubility, pH 6.5	0.049	mg/mL	mann et al., 2005
Intestinal transcellular permeability	1.555e-04	cm/min	Parameter optimization
koff, GABRG2	1	1/min	Parameter optimization
Kd, GABRG2	1.8	nmol/L	Calculated
Km, CYP3A4	4	µmol/L	Zwald et al., 2001
kcat, CYP3A4	8.761	1/min	Parameter optimization
Km, UGT1A4	37.8	µmol/L	Zwald et al., 2001
kcat, UGT1A4	4.759	1/min	Zwald et al., 2001
GFR fraction	0.6401	-	Parameter optimization

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Automated Table of Expression Profiles BB

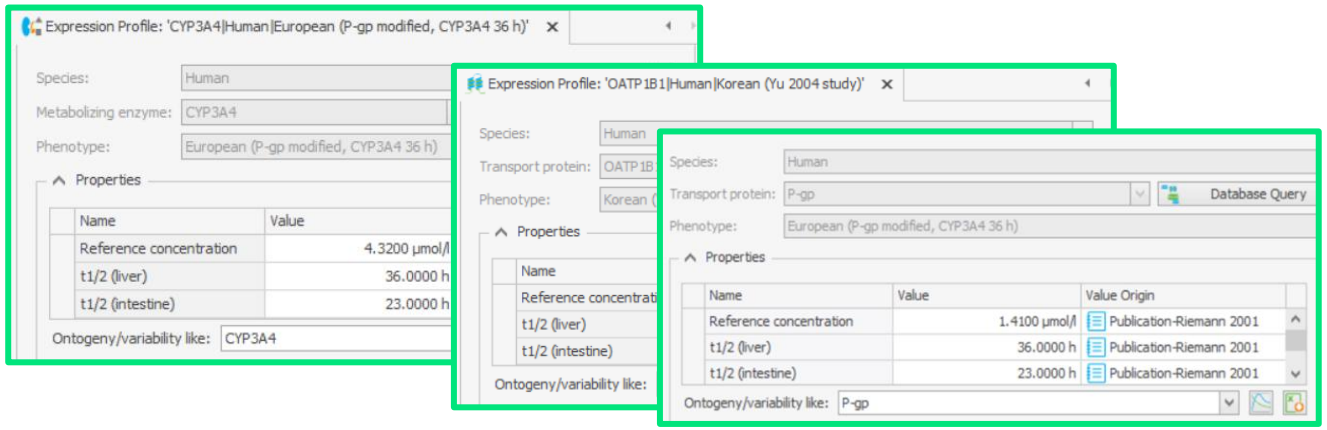

Table of proteins, phenotypes, assays, and ontogeny

Molecule	Phenotype	Assay	Ontogeny/Variability+
Metabolizing Enzymes			
AADAC	European (P-gp modified, CYP3A4 36 h)	EST	No
AADAC	Korean (Yu 2004 study)	EST	No
CYP3A4	European (P-gp modified, CYP3A4 36 h)	RT-PCR	Yes
CYP3A4	Korean (Yu 2004 study)	RT-PCR	Yes
UGT1A4	European (P-gp modified, CYP3A4 36 h)	Array	Yes
Protein Binding Partners			
ATP1A2	European (P-gp modified, CYP3A4 36 h)	EST	No
ATP1A2	Korean (Yu 2004 study)	RT-PCR	No
GABRG2	European (P-gp modified, CYP3A4 36 h)	RT-PCR	No
GABRG2	Korean (Yu 2004 study)	RT-PCR	No
Transporters			
OATP1B1	European (P-gp modified, CYP3A4 36 h)	Array	No
OATP1B1	Korean (Yu 2004 study)	RT-PCR	No
P-gp	European (P-gp modified, CYP3A4 36 h)	Array	Yes

Table of expression profiles parameters

Molecule	Phenotype	Parameter	Value	Unit	Source
Metabolizing Enzymes					
AADAC	European (P-gp modified, CYP3A4 36 h)	Reference concentration	1	µmol/L	Assumed
	European (P-gp modified, CYP3A4 36 h)	t1/2 (liver)	36	h	Berg et al., 2004
	European (P-gp modified, CYP3A4 36 h)	t1/2 (intestine)	23	h	Berg et al., 2004
	Korean (Yu 2004 study)	Reference concentration	1	µmol/L	PK-Sim default
	Korean (Yu 2004 study)	t1/2 (liver)	36	h	Hu et al., 2018
	Korean (Yu 2004 study)	t1/2 (intestine)	23	h	Hu et al., 2018
CYP3A4	European (P-gp modified, CYP3A4 36 h)	Reference concentration	4.32	µmol/L	Utkin 2001
	European (P-gp modified, CYP3A4 36 h)	t1/2 (liver)	36	h	Utkin 2001
	European (P-gp modified, CYP3A4 36 h)	t1/2 (intestine)	23	h	Utkin 2001
	Korean (Yu 2004 study)	Reference concentration	3.63	µmol/L	Parameter optimization
	Korean (Yu 2004 study)	t1/2 (liver)	36	h	Assumed
	Korean (Yu 2004 study)	t1/2 (intestine)	23	h	Assumed

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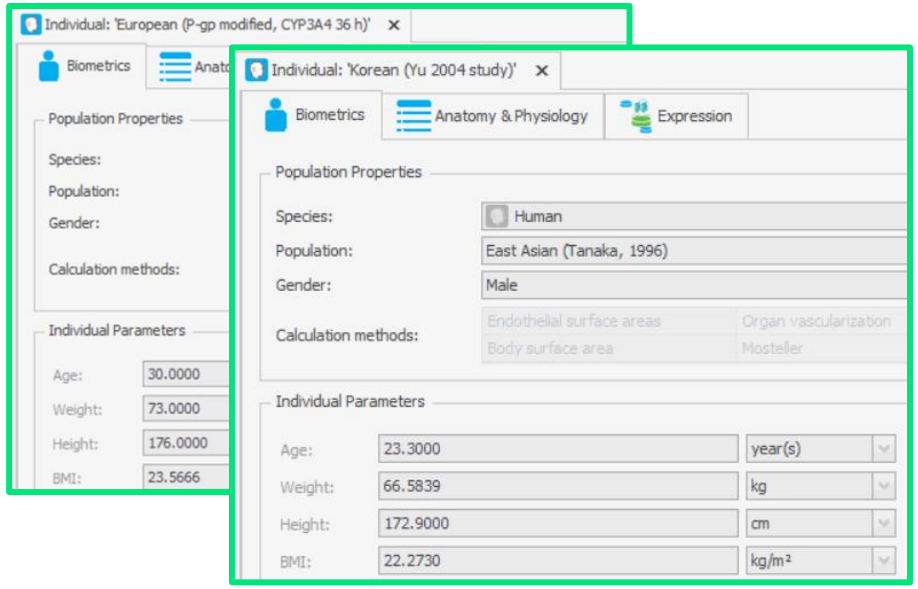
Automated Table of Individuals and Populations BB



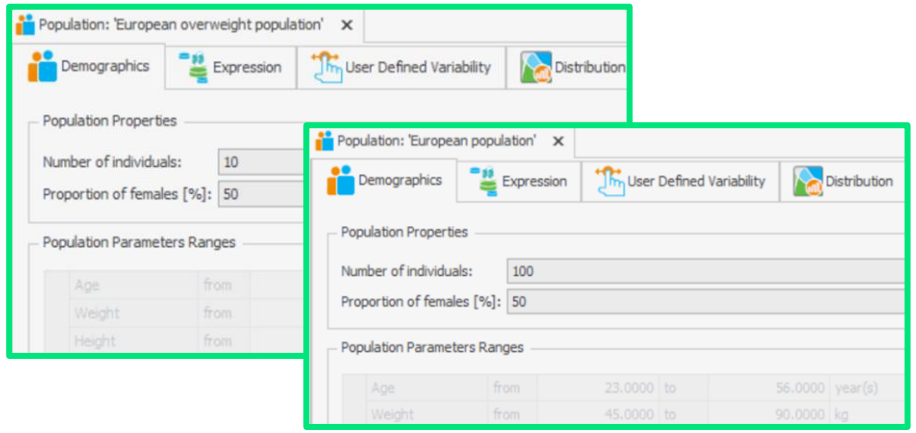


Table of individual characteristics

Individual name	Age [year(s)]	Weight [kg]	Height [cm]	BMI [kg/m^2]	Gender	Database	Expression*
European (P-gp modified, CYP3A4 36 h)	30	73.0	176	23.6	Male	European	CYP3A4/European (P-gp modified, CYP3A4 36 h), P-gp/European (P-gp modified, CYP3A4 36 h)
Korean (Yu 2004 study)	23.3	66.9	173	22.4	Male	East Asian	CYP3A4/Korean (Yu 2004 study), AADAC/Korean (Yu 2004 study), OATP1B1/Korean (Yu 2004 study), GABRG2/Korean (Yu 2004 study)

Table of population characteristics

Population name	Age [year(s)]	Weight [kg]	Height [cm]	BMI [kg/m^2]	Number of individuals	Proportion of females [%]	Based on individual
European overweight population	69.0 [19.7%] 70.2 [13.8] 54.5, 90.3 45-98	80.1 [17.6%] 81.1 [14.2] 70.2, 107 70-140	16.2 [5.39%] 16.2 [0.871] 15.2, 17.3 150-180	30.7 [19.4%] 31.2 [6.06] 24.4, 40.7 23.7-44.3	10	50	European (P-gp modified, CYP3A4 36 h)
European population	38.4 [24.6%] 39.7 [9.76] 23.9, 53.8 23-56	67.8 [15.7%] 68.7 [10.8] 52.7, 87.6 45-90	168 [7.25%] 168 [12.2] 153, 189 133-198	24.1 [12.4%] 24.3 [3.00] 20.9, 29.3 18.9-39.9	100	50	European (P-gp modified, CYP3A4 36 h)

*The first line for each population characteristics showed geometric mean [coefficient of variation %]
The second line for each population characteristics showed mean [standard deviation]
The third line for each population characteristics showed 5th percentile, 95th percentile
The fourth line for each population characteristics showed minimum-maximum

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Automated Table of Other BB

Parameter	Value	Unit	Source
Tablet (Lint80)			
Dissolution time (80% dissolved)	240	min	Hu et al., 2005
Lag time	12	min	Hu et al., 2005
Use as suspension	yes	-	Hu et al., 2005
Tablet (Weibull)			
Dissolution time (50% dissolved)	0.0107	min	Parameter optimization
Lag time	0	min	Assumed
Dissolution shape	4.38	-	Parameter optimization
Use as suspension	yes	-	Wang et al., 2022

Parameter	Name/Value [unit]
iv 0.001 mg (5 min)	
Scheme item 1	
Application type	Intravenous
Start time	0 [h]
Dose	0.001 [mg]
Number of repetitions	1 [-]
Time Between repetitions	0 [h]
Mikus 2017	
Scheme item 1	
Application type	Intravenous
Start time	6 [h]
Dose	2 [mg]
Number of repetitions	1 [-]
Time Between repetitions	0 [h]
Scheme item 2	
Application type	Oral
Formulation	Tablet (Weibul)
Start time	0 [h]
Dose	4 [mg]
Number of repetitions	1 [-]
Time Between repetitions	0 [h]

BB Data Presentation as Text Blocks

Metabolizing Enzymes kinetics

In the final PBPK model:

- ExampleDrug:
  - is metabolized by CYP3A4 via *in-vitro* metabolic rate in the presence of liver microsomes- Michaelis-Menten process with parameters Km = 4 µmol/L and kcat = 8.761 1/min.
  - is metabolized by UGT1A4 via *in-vitro* metabolic rate in the presence of liver microsomes- Michaelis-Menten process with parameters Km = 37.8 µmol/L and kcat = 4.759 1/min.

Renal/hepatic/biliary kinetics

- ExampleDrug:
  – is cleared renally via glomerular filtration process with parameter GFR fraction = 0.6401.

Events BB

In the final PBPK model, 3 events were created as listed below:

- Gallbladder emptying enabled.
- High-fat breakfast (from High-fat breakfast template) with Meal energy content 800 kcaL (other parameter(s) is(are) as default values in Table 15).
- Urinary bladder emptying with fraction 0.5 enabled.

Summary

- **This work is part of the Boehringer Ingelheim PBPK Automated Report Generator Project, which aims to facilitate and accelerate PK-Sim®-related reporting.**

- The OSP suite R packages serve as a bridge between PK-Sim models and automated reporting workflows.

- **osp.snapshots** R package:
  - Extracts data from PK-Sim BBs and converts them into data frames
  - Enables simulation computation (via ospsuite R) and generates simulation plots (teaser in the next slide)

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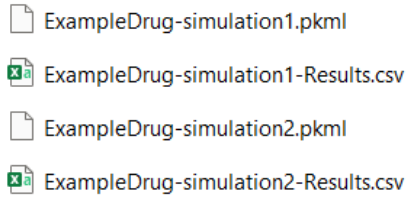
What's next? Generating simulation plots

Step 1: running simulations from snapshots + storing the results for faster loading

```
simulations_results <-  get_simulations_results(
                            snapshot = snapshot,
                            output_dir =
                            here::here("path/to/simulationResults"),
                            load_results = TRUE
                            )
```

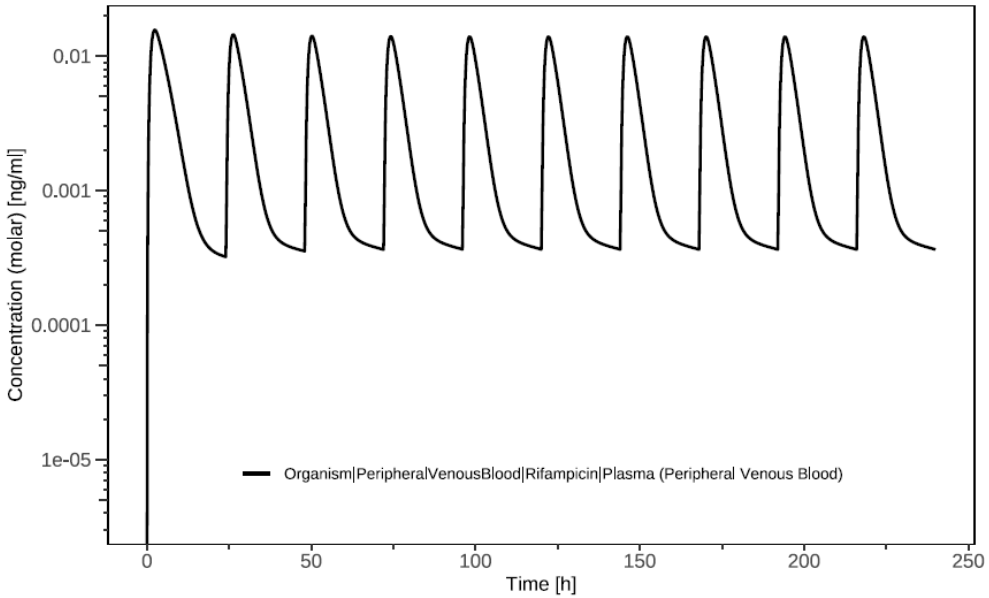
```
"Simulations": [
    {
      "Name": "simulation1",
      "Model": "4Comp",
      "ObservedData": [...],
      "Solver": {...},
      "OutputSchema": [...],
      "Parameters": [...],
      "OutputSelections": [...],
      "OutputMappings": [...],
      "Individual": "...",
      "Compounds": [...],
      "Events": [...],
      "ObserverSets": [...],
      ...
    }
]
```

There is more to come



Step 2: plotting time profiles

```
generate_plot(  simulations_results = simulations_results,
                            simulation_name = "simulation1",
                            plot_name = "Time Profile Analysis")
```



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Acknowledgement

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  - Hugo Maas
  - Jan-Georg Wojtyniak

- ESQlabs Software Team & others

- OSP community

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