

Tools and workflows for automated reporting of PBPK modeling with OSP

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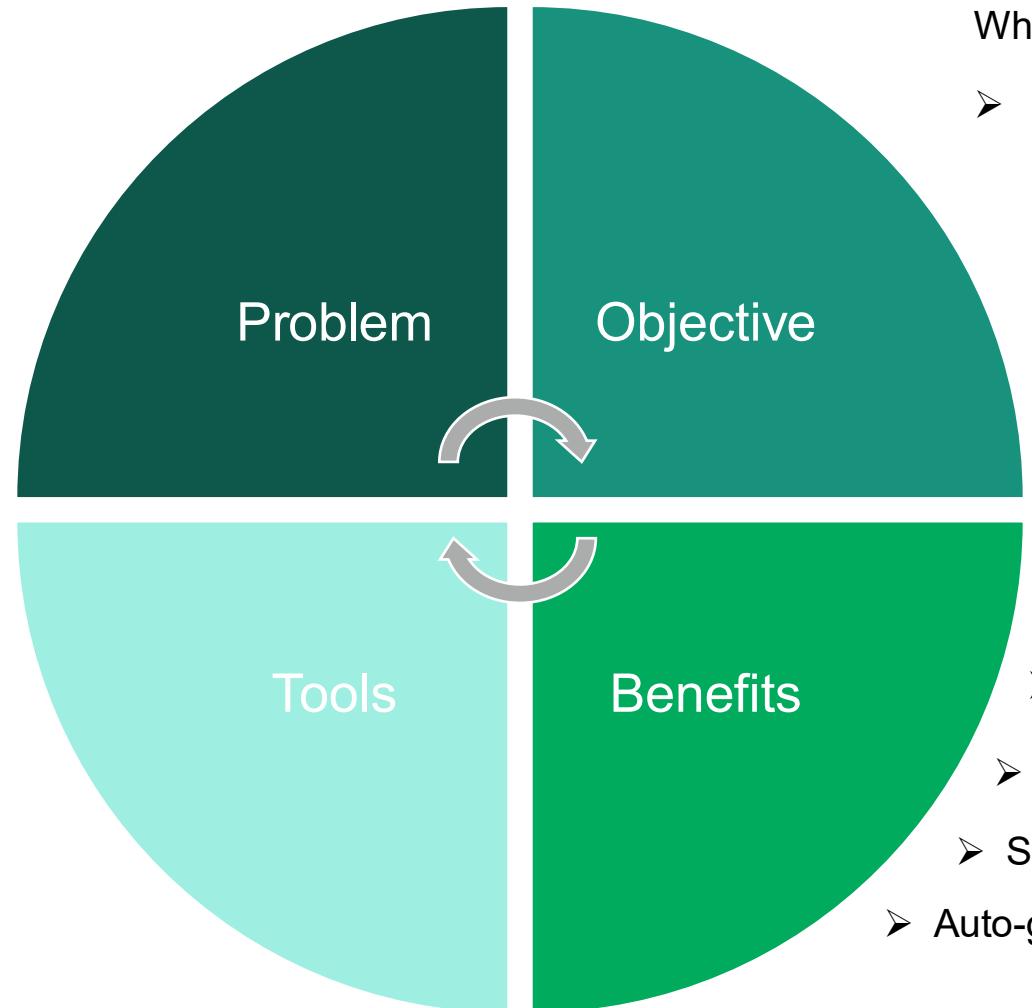
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PBPK Automated Reporting: Why, what and how

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.



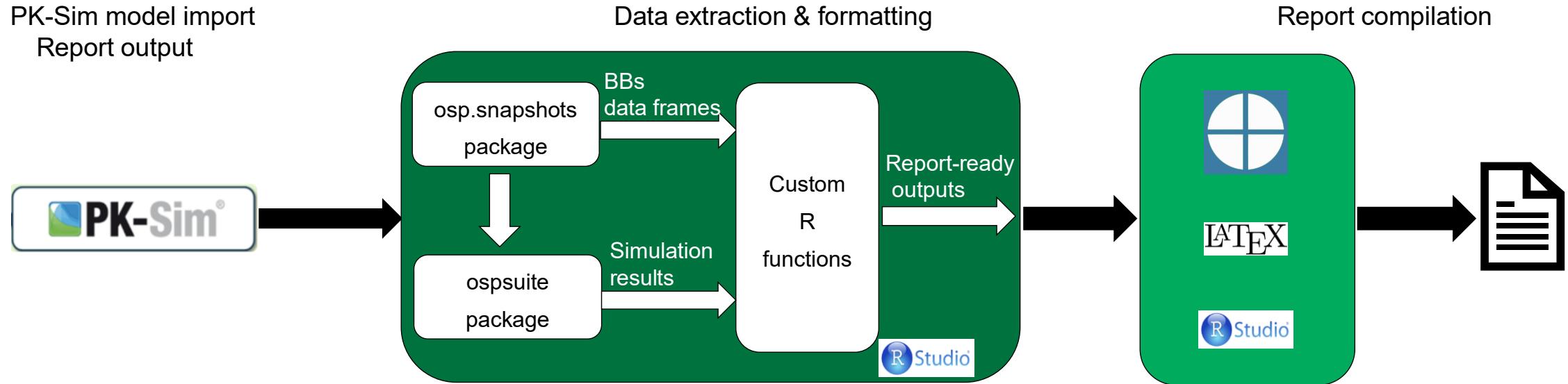
What:

- Within **Boehringer Ingelheim**, automation techniques were implemented to **enhance the efficiency** of PBPK report generation.
- Faster reporting
- Consistent quality
- Fewer manual errors
- Simplified QC process
- Auto-generated figures and tables

How:

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

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": [...],  
        ...  
    }  
]
```

Is small molecule
Lipophilicity:
Experiment Lipophilicity Value Origin
Optimized 2.8972 Log Units Parameter Identification-Par...

Fraction unbound (plasma, reference value):
Binds to: Albumin α1-acid glycoprotein Unknown
Experiment Fraction Unbound Species Value Origin
Gertz et al. 2010 0.0310 Human Parameter Identific...

Molecular weight:
Molecular weight 325.7800 g/mol
Has halogens Yes
Effective molecular weight 286.7800 g/mol
Value origin Publication-Hu et al., 2005

Compound type / pKa:
Base 6.2000
Add 10.9500
Neutral <None>
Value origin Publication-Wang et al., 2024

Solubility:
Experiment Solubility at Re... Ref-pH Solubility gain p... pH-dependent ... Value Origin
FaSSIF 0.0490 mg/ml 6.5000 1000.0000 Show Graph Publicat...
Parameter Identification

intermediate: osp.s 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	Parameter	Value	Unit
ExampleDrug	physicochemical_property	pKa	acid	10.95	2.897	Log Units	Source
ExampleDrug	physicochemical_property	solubility	pH 6.5	0.049	0.031	-	Parameter optimization
ExampleDrug	physicochemical_property	intestinal_permeability	Optimized	0.0001555	0.049	mg/mL	Parameter optimization
ExampleDrug	protein_binding_partners	SpecificBinding	koff, GABRG2	37.8	325.8	g/mol	Hu et al., 2005
ExampleDrug	protein_binding_partners	SpecificBinding	Kd, GABRG2	1.8	1	-	Hu et al., 2005
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	Km, CYP3A4	4.759	1	-	Hu et al., 2005
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	kcat, CYP3A4	8.761	1	-	Hu et al., 2005
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	Km, UGT1A4	37.8	10.95	-	Wang et al., 2024
ExampleDrug	metabolizing_enzymes	MetabolizationLiverMicrosomes_MM	kcat, UGT1A4	4.759	0.049	mg/mL	Wang et al., 2024
ExampleDrug	renal_clearance	GlomerularFiltration	GFR fraction	0.6401	0.0001555	cm/min	mann et al., 2005

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	0.0001555	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

Automated Table of Expression Profiles BB

The figure shows three overlapping software windows, each representing an expression profile:

- CYP3A4 Human | European (P-gp modified, CYP3A4 36 h)**: Species: Human, Metabolizing enzyme: CYP3A4, Phenotype: European (P-gp modified, CYP3A4 36 h). Properties table includes: Reference concentration (4.3200 μmol/L), t_{1/2} (liver) (36.0000 h), t_{1/2} (intestine) (23.0000 h). Ontogeny/variability like: CYP3A4.
- OATP1B1 Human | Korean (Yu 2004 study)**: Species: Human, Transport protein: OATP1B1, Phenotype: Korean (Yu 2004 study). Properties table includes: Reference concentration (1.4100 μmol/L), t_{1/2} (liver) (36.0000 h), t_{1/2} (intestine) (23.0000 h). Ontogeny/variability like: P-gp.
- P-gp Human | European (P-gp modified, CYP3A4 36 h)**: Species: Human, Transport protein: P-gp, Phenotype: European (P-gp modified, CYP3A4 36 h). Properties table includes: Reference concentration (1.4100 μmol/L), t_{1/2} (liver) (36.0000 h), t_{1/2} (intestine) (23.0000 h). Ontogeny/variability like: P-gp.

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)	t _{1/2} (liver)	36	h	Berg et al., 2004
	European (P-gp modified, CYP3A4 36 h)	t _{1/2} (intestine)	23	h	Berg et al., 2004
	Korean (Yu 2004 study)	Reference concentration	1	μmol/L	PK-Sim default
	Korean (Yu 2004 study)	t _{1/2} (liver)	36	h	Hu et al., 2018
	Korean (Yu 2004 study)	t _{1/2} (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)	t _{1/2} (liver)	36	h	Utkin 2001
	European (P-gp modified, CYP3A4 36 h)	t _{1/2} (intestine)	23	h	Utkin 2001
	Korean (Yu 2004 study)	Reference concentration	3.63	μmol/L	Parameter optimization
	Korean (Yu 2004 study)	t _{1/2} (liver)	36	h	Assumed
	Korean (Yu 2004 study)	t _{1/2} (intestine)	23	h	Assumed

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

Automated Table of Individuals and Populations BB

Individual: 'European (P-gp modified, CYP3A4 36 h)' x

Biometrics **Anatomy & Physiology**

Population Properties

Species: Human

Population: East Asian (Tanaka, 1996)

Gender: Male

Calculation methods:

Age: 30.0000	Weight: 73.0000
Height: 176.0000	BMI: 23.5666

Individual Parameters

Age: 23.3000	year(s)
Weight: 66.5839	kg
Height: 172.9000	cm
BMI: 22.2730	kg/m ²

Population: 'European overweight population' x

Demographics **Expression** **User Defined Variability** **Distribution**

Population Properties

Number of individuals: 10

Proportion of females [%]: 50

Population Parameters Ranges

Age from	23.0000	to	56.0000	year(s)
Weight from	45.0000	to	90.0000	kg
Height from				

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

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 (Weibull)
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 $K_m = 4 \mu\text{mol/L}$ and $k_{cat} = 8.761 \text{ 1/min.}$
 - is metabolized by UGT1A4 via *in-vitro* metabolic rate in the presence of liver microsomes- Michaelis-Menten process with parameters $K_m = 37.8 \mu\text{mol/L}$ and $k_{cat} = 4.759 \text{ 1/min.}$

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)

What's next? Generating simulation plots

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

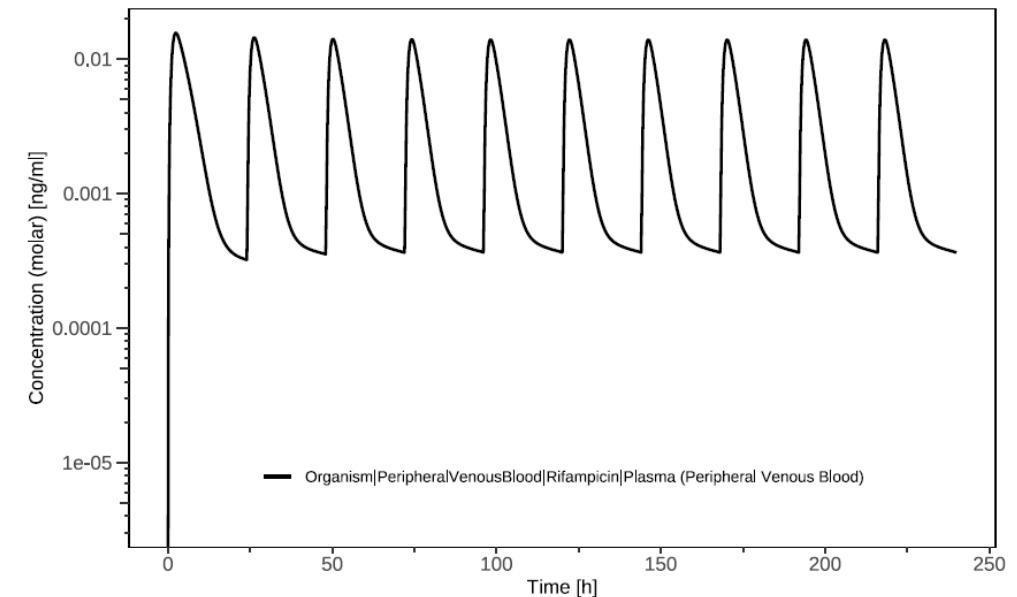
```
simulations_results <- get_simulations_results(  
    snapshot = snapshot,  
    output_dir =  
        here::here("path/to/simulationResults"),  
    load_results = TRUE  
)  
  
"Simulations": [  
  {  
    "Name": "simulation1",  
    "Model": "4Comp",  
    "ObservedData": [...],  
    "Solver": {...},  
    "OutputSchema": [...],  
    "Parameters": [...],  
    "OutputSelections": [...],  
    "OutputMappings": [...],  
    "Individual": "...",  
    "Compounds": [...],  
    "Events": [...],  
    "ObserverSets": [...],  
    ...  
  }  
]
```

There is more to come

- 📄 ExampleDrug-simulation1.pkml
- 📄 ExampleDrug-simulation1-Results.csv
- 📄 ExampleDrug-simulation2.pkml
- 📄 ExampleDrug-simulation2-Results.csv

Step 2: plotting time profiles

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



Acknowledgement

- Boehringer Ingelheim:
 - Ibrahim Ince
 - PBPK/QSP modeling team members
 - Steve Choy
 - Hugo Maas
 - Jan-Georg Wojtyniak
- ESQlabs Software Team & others
- OSP community

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