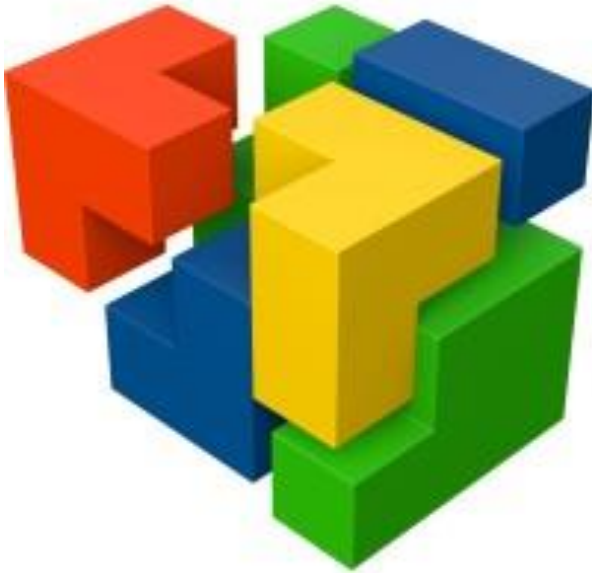


# OSMOSES

Modularization and Qualification of complex  
PB-QSP models with OSP version 12

Pavel Balazki @OSP Community Conference 2024

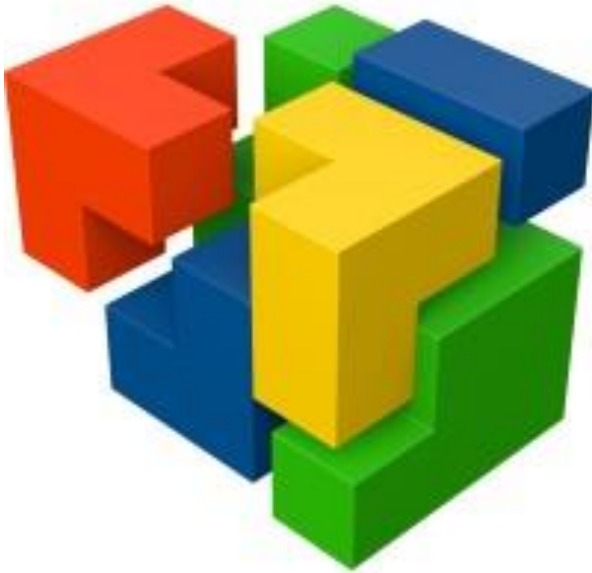




# OSMOSES

Modularization of PB-QSP projects as a solution for

- 1) Management of ever-growing model complexity
- 2) Model re-usability
- 3) Automated (re-)qualification



# OSMOSES



OSPS Version 12

Modularization of PB-QSP projects as a solution for

- 1) Management of ever-growing model complexity
- 2) Model re-usability
- 3) (Automated (re-)qualification)

# Acknowledgements

Collaborators & Sponsors

## Sponsors



# Acknowledgements

## Collaborators & Sponsors

### Sponsors



Federal Ministry  
of Education  
and Research



### Developers

- Juri Solodenko
- Michael Sevestre
- Robert McIntosh
- Benjamin Mariano Perez
- Abdel Rodriguez (former)
- Georgios Daskalakis (former)



DESIGN{2}CODE



# Acknowledgements

Collaborators & Sponsors

## Sponsors



Federal Ministry  
of Education  
and Research



**sanofi**



## Model library contributors

University of Saarland,  
Clinical Pharmacy (Prof. Dr. Thorsten Lehr)



UNIVERSITÄT  
DES  
SAARLANDES

# 01

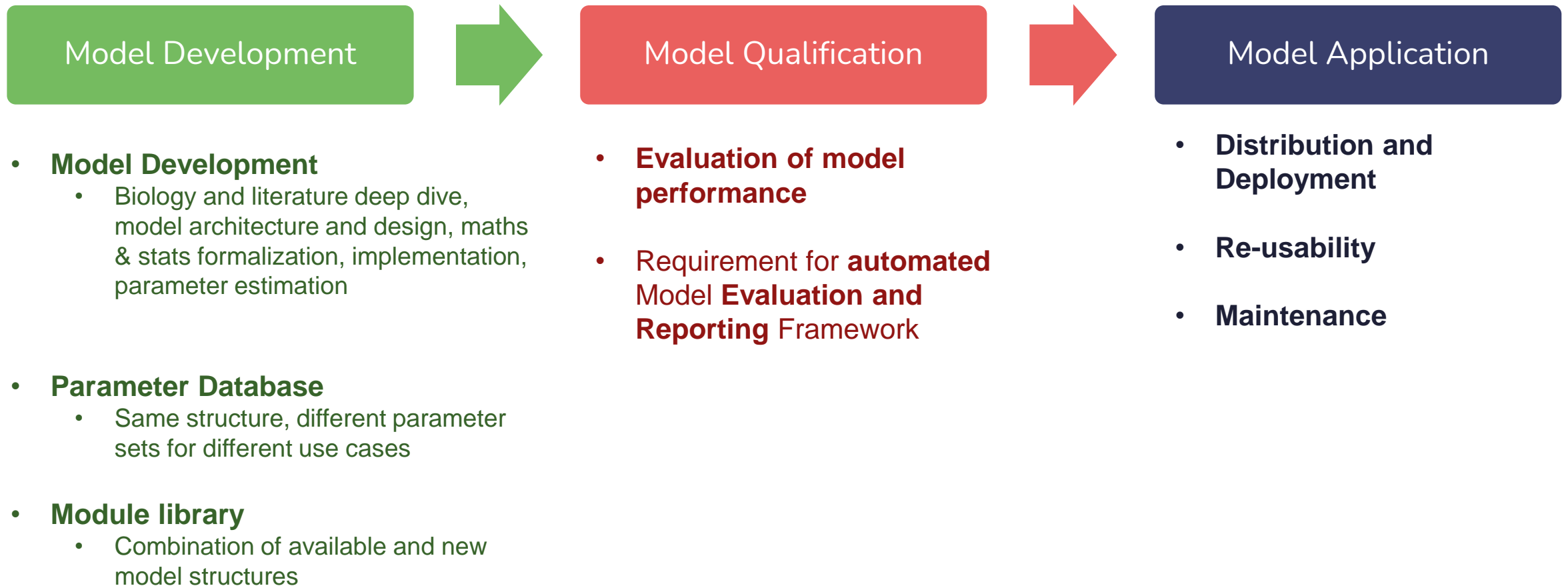
## QSP model lifecycle

Need for new approaches



# Model management through the entire lifecycle

## Development, Qualification, and Application & Delivery





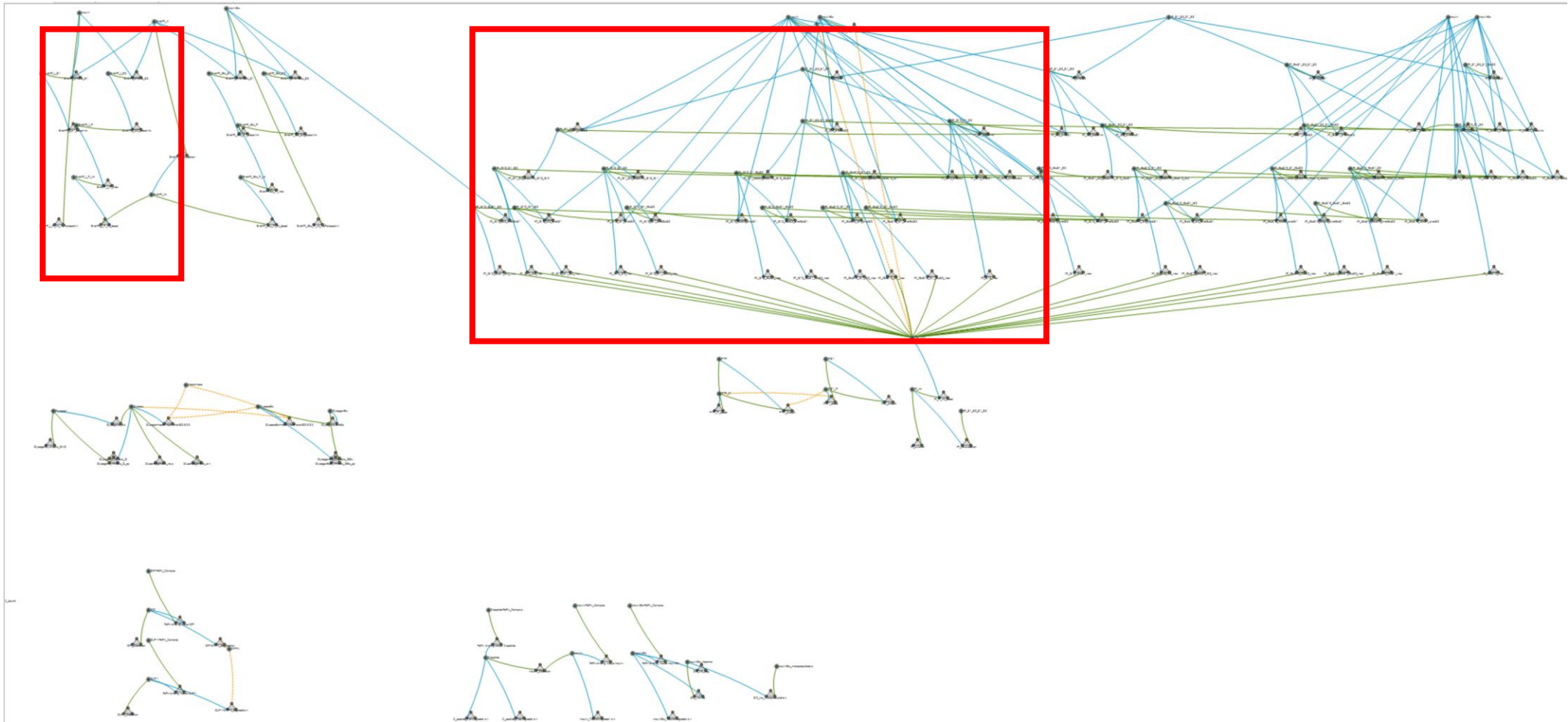
# Problem: high model complexity

- Growing model complexity makes maintenance and debugging challenging
  - Both during model development and application

# Problem: high model complexity

Example – Diabetes Platform

○ G



# Problem: re-usability

- Growing model complexity makes maintenance and debugging challenging
- Models are developed for a specific use case with limited re-usability, or...

# Problem: re-usability

- Growing model complexity makes maintenance and debugging challenging
- Models are developed for a specific use case with limited re-usability, or...
- Integration into new models is tedious and requires multiple manual steps

# Problem: re-usability

- Growing model complexity
- Models are developed in isolation
- Integration into new models

AndreDlm Add files via upload 4f88e0f · 2 months ago 55 Commits

BuildingBlocks	Add files via upload	2 months ago
CotyledonPerfusionModel	Adds in silico cotyledon perfusion model and updates READ...	3 years ago
Models	Adds acetaminophen pkml files	3 years ago
ModelStructure.png	Corrected figure	3 years ago
MoleculeBB_FetalFractionUnbound.png	Updated README	3 years ago
README.md	Update README.md	last year

README

## Physiologically Based Pharmacokinetic Models for Pregnancy

Within this repository, we distribute the physiologically-based whole-body models for pregnant individuals published in [\[1,2,3,4,5,6,7\]](#). Additionally, this repository contains the refined passive transports building block which was used to build pregnancy PBPK models with different unbound drug fractions in maternal and fetal organism as described in [\[8\]](#) as well as the *in silico* cotyledon perfusion model presented in [\[9\]](#).

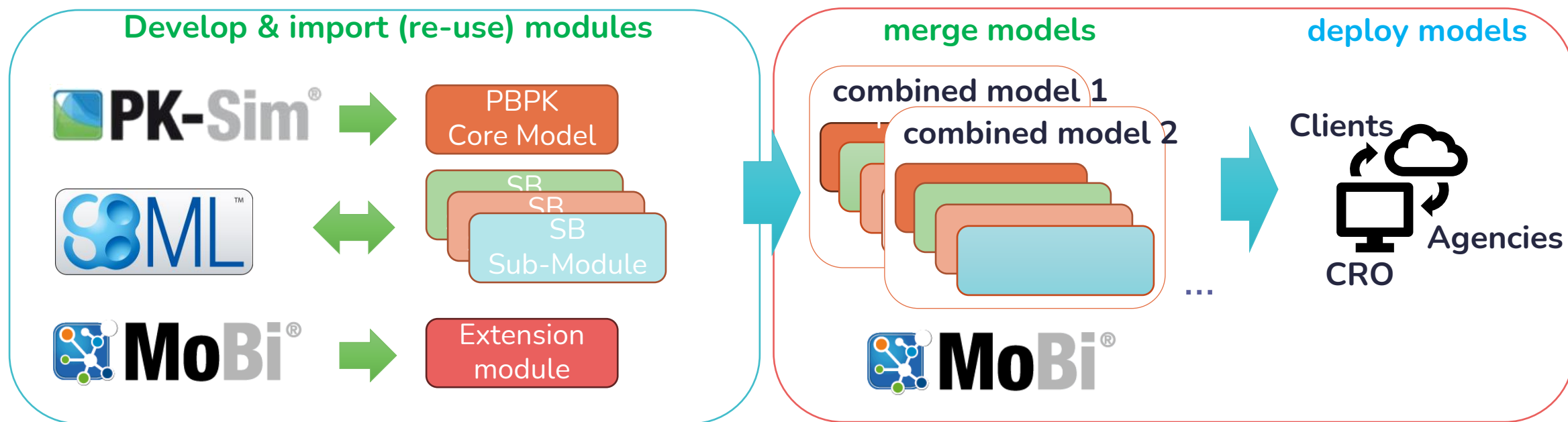
The pregnancy (and postpartum) PBPK model for amoxicillin published in [\[10\]](#) can be found [here](#).

The pregnancy model structure comprises per default 27 compartments, including nine pregnancy-specific compartments as shown in the schema below.

# Problem: maintenance

- Growing model complexity makes maintenance and debugging challenging
- Models are developed for a specific use case with limited re-usability, or...
- Integration into new models is tedious and requires multiple manual steps
- Maintenance (e.g., update to new PK-Sim version)

# The future of QSP Platform management - Modularization



# 02

## **Modularization**

Implementation in OSPS v12



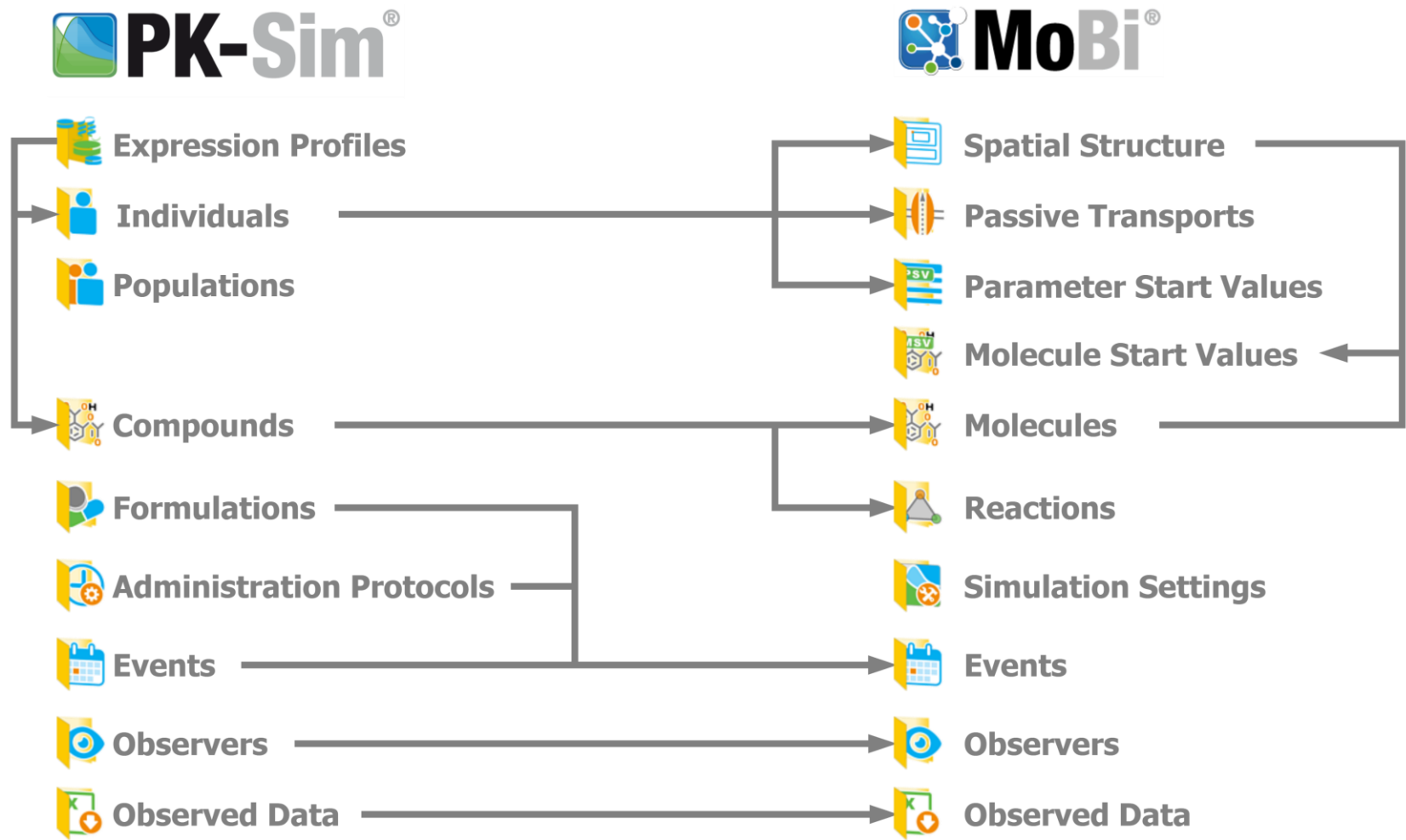


Version 12 is work in progress

Shown GUI and functionality may change  
in the final release

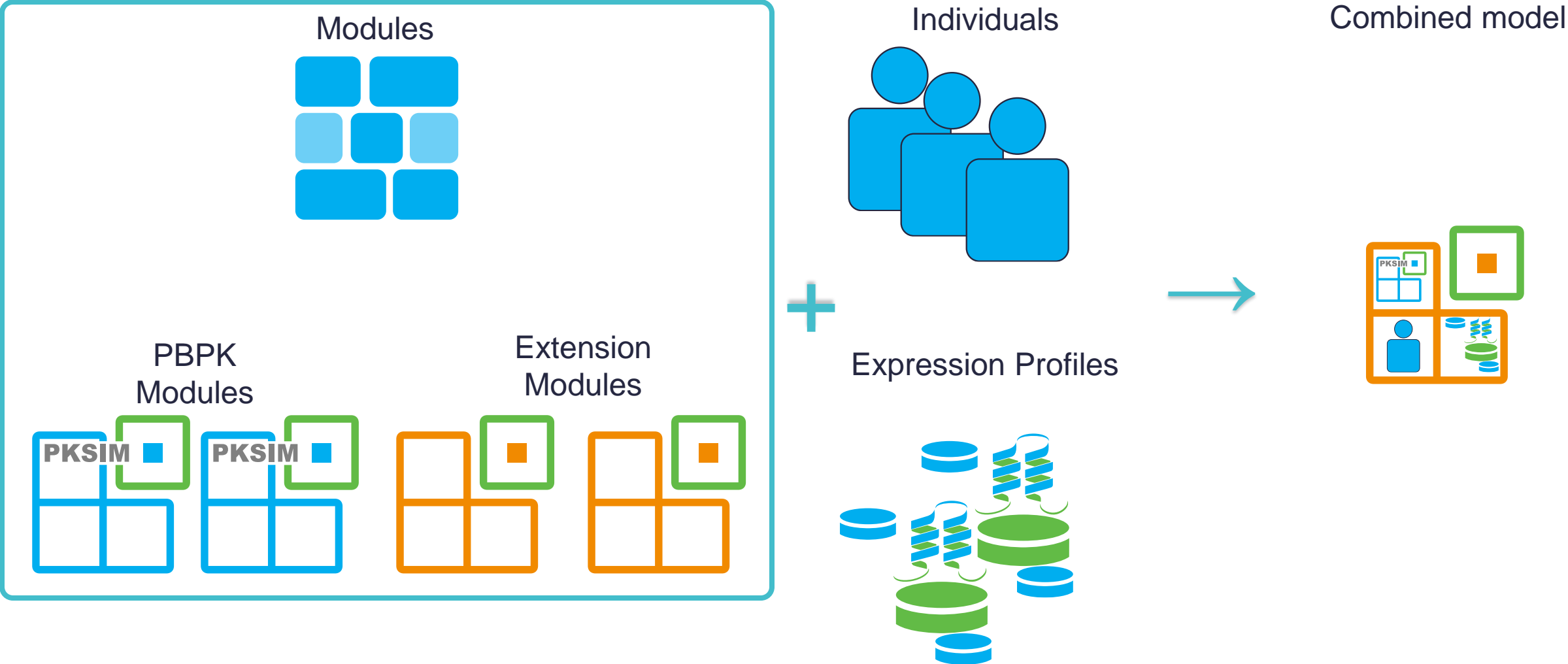
# Project organization

Status quo (<v12)



# Project organization

MoBi v12

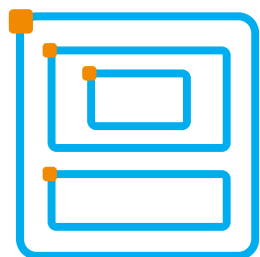
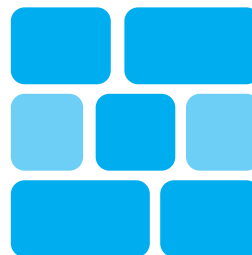




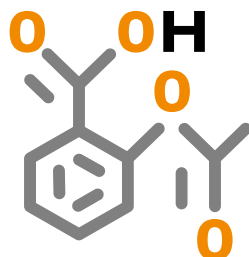
# Project organization

MoBi v12

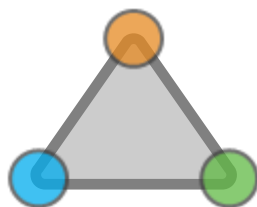
A module



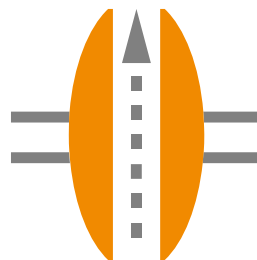
Spatial Structure



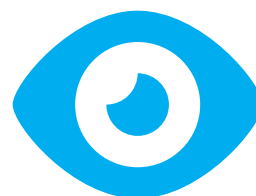
Molecules



Reactions



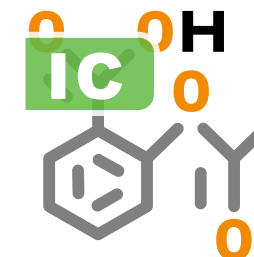
Passive  
Transports



Observers



Events



Initial Conditions



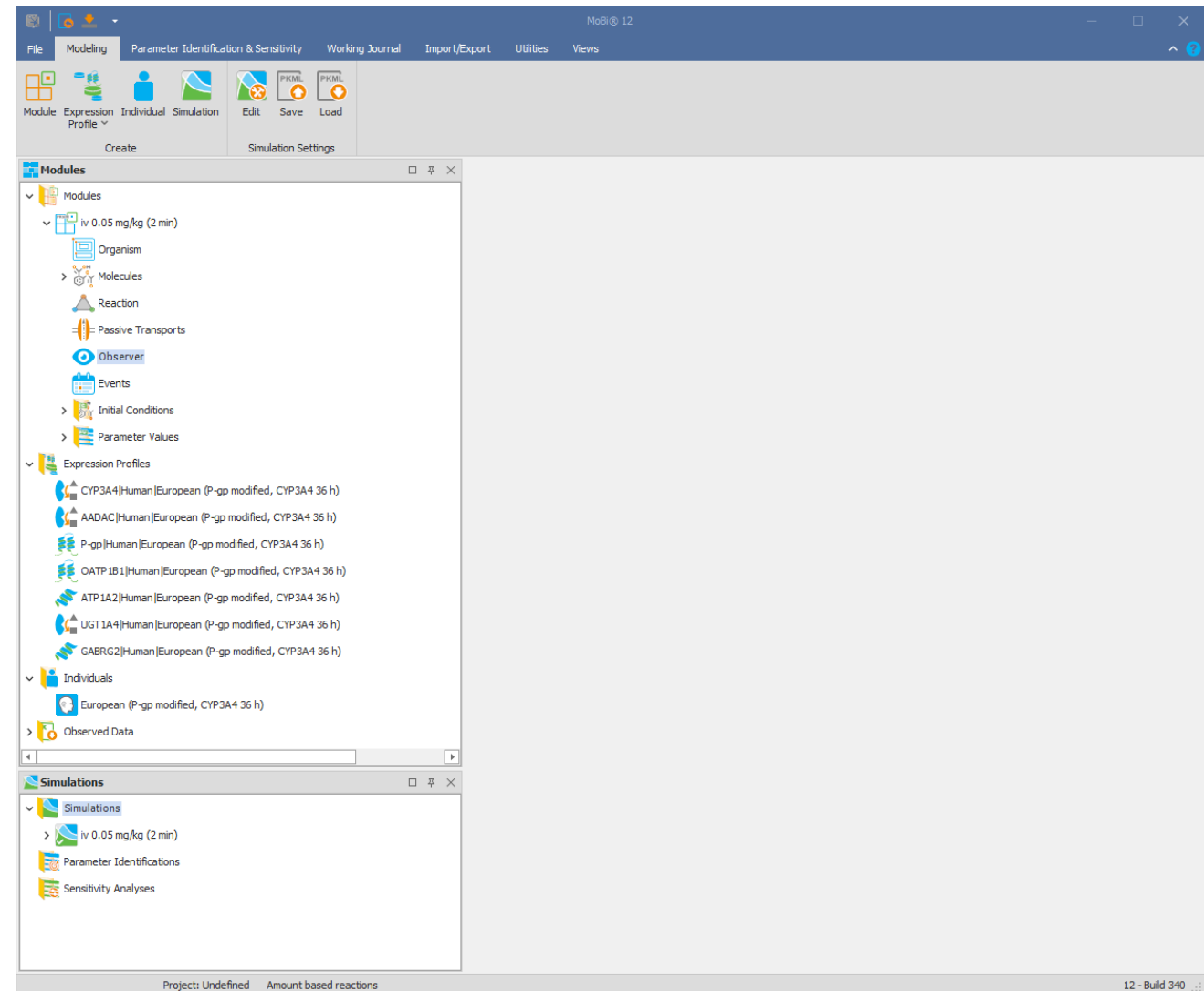
Parameter Values



# Project organization

## PK-Sim to MoBi transfer

- One PK-Sim module
- Expression Profile(s)
- Individuals



# Individuals



Create Individual

Name:

Biometrics

Anatomy & Physiology

Population Properties

Species: 

Human

Population: 

European (ICRP, 2002)

Gender: 

Male

Calculation methods:

Endothelial surface areas

Organ vascularization

Body surface area

Mosteller

Individual Parameters

Age: 

30.00

year(s)

Weight: 

73.00

kg

Height: 

176.00

cm

BMI: 

23.57

kg/m<sup>2</sup>

Value origin:

Mean

Disease State

Healthy

Healthy individuals in PK-Sim are representative of the general population of individuals in the specified ethnicity and/or geographic area. These individuals are parameterized under the assumption that they have no chronic or comorbid disease states that would have a relevant effect on anatomy, physiology or drug disposition.

Previous

Next

OK

Cancel

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

Parameters

Formulas

Origin Data

Species: 

Human

Gender: 

Male

Age: 

30.0000 year(s)

Gestational age: 

2087.1429 week(s)

Height: 

176.0000 cm

Weight: 

73.0000 kg

Population: 

European (ICRP, 2002)

Endothelial surface areas: 

Organ vascularization

Body surface area: 

Mosteller

PK-Sim Version: 

12.0

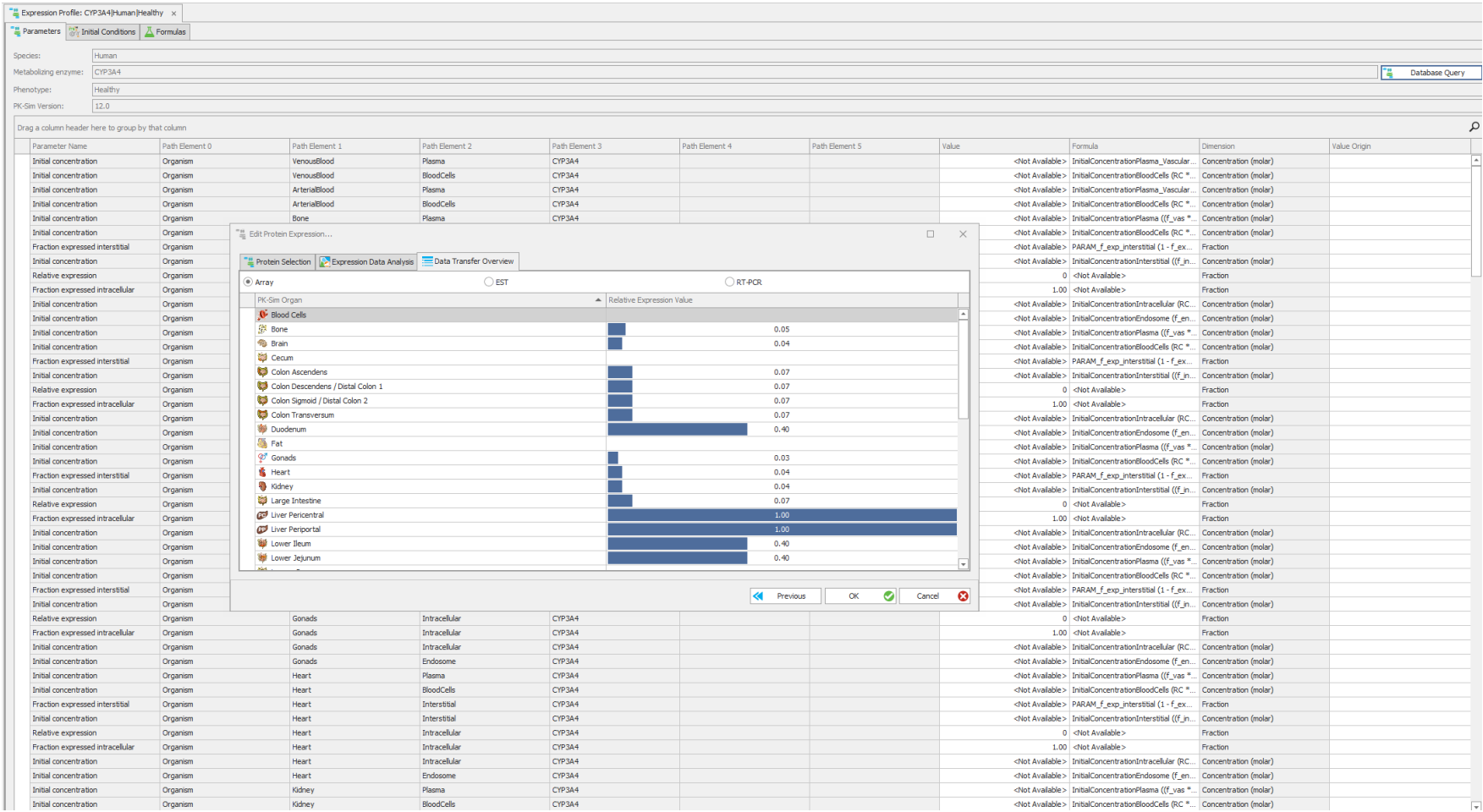
Parameters

Drag a column header here to group by that column

Parameter Name	Path Element 0	Path Element 1	Path Element 2	Path Element 3	Value	Formula	Dimension	Value Origin
Ontogeny factor (albumin)	Organism				<Not Available>	TableFormulaWithXArgum...	Dimensionless	
Ontogeny factor (alpha-1...	Organism				<Not Available>	TableFormulaWithXArgum...	Dimensionless	
Ontogeny factor (alpha-1...	Organism				<Not Available>	Ontogeny for alpha-1-acid gly...	Dimensionless	
Ontogeny factor (albumin...	Organism				<Not Available>	Ontogeny for Albumin - Pl...	Dimensionless	
BMI	Organism				<Not Available>	PARAM_BMI (Height)>0 ? ...	BMI	Other-Standard definition
Post menstrual age	Organism				<Not Available>	PARAM_PostMenstrualAg...	Age in years	
BSA	Organism				<Not Available>	PARAM_BSA (1.6667 * W...	Area	
pH (blood cells)	Organism				7.22	<Not Available>	Dimensionless	Publication-ICRP, 2002. ...
pH (plasma)	Organism				7.40	<Not Available>	Dimensionless	Publication-ICRP, 2002. ...
Age	Organism				30.00 year(s)	<Not Available>	Age in years	
Gestational age	Organism				40.00 week(s)	<Not Available>	Age in weeks	
Vf (lipid, plasma)	Organism				7.00E-3	<Not Available>	Dimensionless	Publication-ICRP, 2002. ...
Vf (neutral lipid, plasma)-...	Organism				3.20E-3	<Not Available>	Dimensionless	Publication-Rodgers T, R...
Vf (protein,plasma)	Organism				0.07	<Not Available>	Dimensionless	Publication-ICRP, 2002. ...
Vf (water,plasma)	Organism				0.93	<Not Available>	Dimensionless	Publication-ICRP, 2002. ...
Surface/Volume ratio (blo...	Organism				16700.00 1/cm	<Not Available>	Inversed length	
Vf (neutral lipid, plasma)-PT	Organism				3.50E-3	<Not Available>	Dimensionless	
Vf (neutral phospholipid, ...	Organism				2.10E-3	<Not Available>	Dimensionless	Publication-Rodgers T, R...
Height	Organism				176.00 cm	<Not Available>	Length	
Vf (neutral lipid, blood cell...	Organism				1.20E-3	<Not Available>	Dimensionless	Publication-Rodgers T, R...
Vf (phospholipid, plasma)...	Organism				2.25E-3	<Not Available>	Dimensionless	
Vf (neutral phospholipid, ...	Organism				3.30E-3	<Not Available>	Dimensionless	Publication-Rodgers T, R...
Vf (water,plasma)-PT	Organism				0.95	<Not Available>	Dimensionless	
Acidic phospholipids (bloo...	Organism				0.57	<Not Available>	Dimensionless	Publication-Rodgers T, R...
Vf (intracellular water, bl...	Organism				0.63	<Not Available>	Dimensionless	Publication-Rodgers T, R...
Hematocrit	Organism				0.47	<Not Available>	Dimensionless	

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# Expression Profiles





# Project organization

Examples of combination

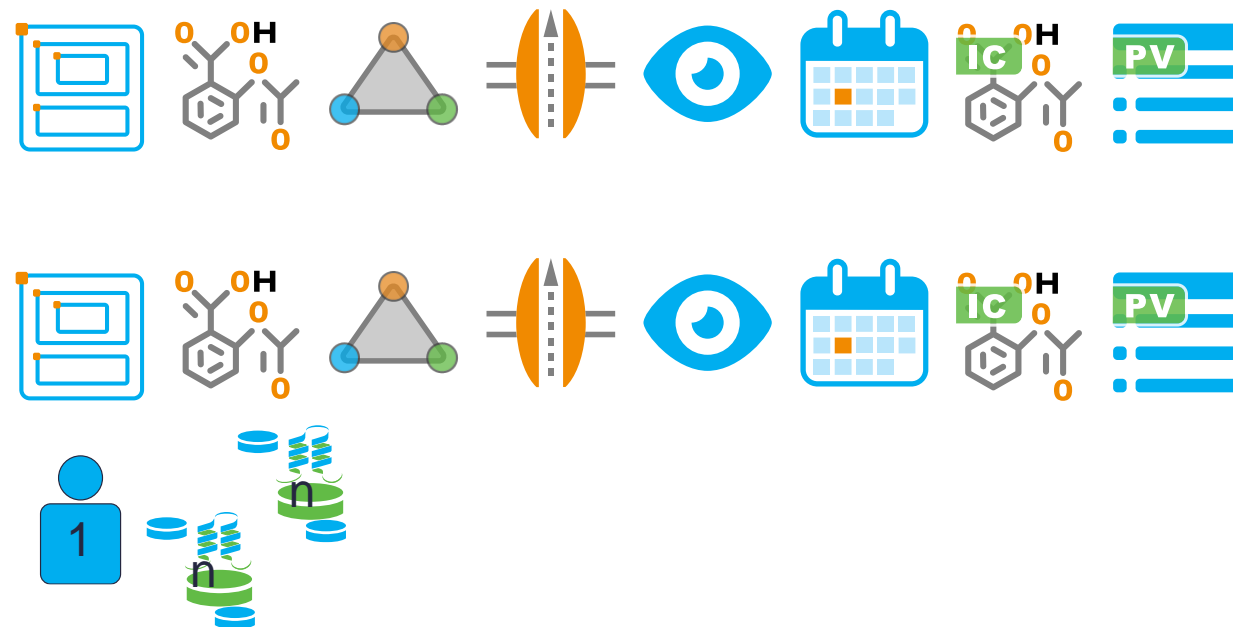


CompoundA



CompoundB

30 years old male  
Normal metabolizer







# Project organization

Examples of combination

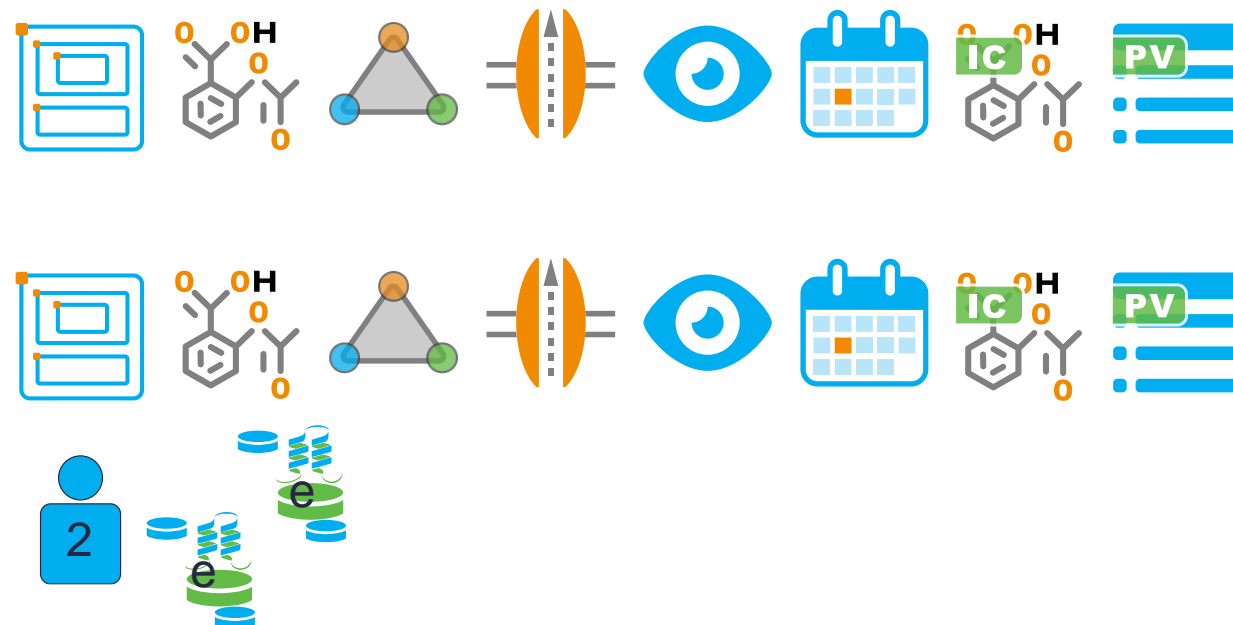


CompoundA



CompoundB

31 years old female  
Extensive metabolizer





# Project organization

Examples of combination

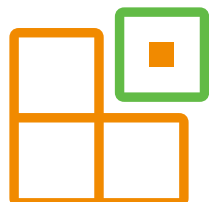


CompoundA

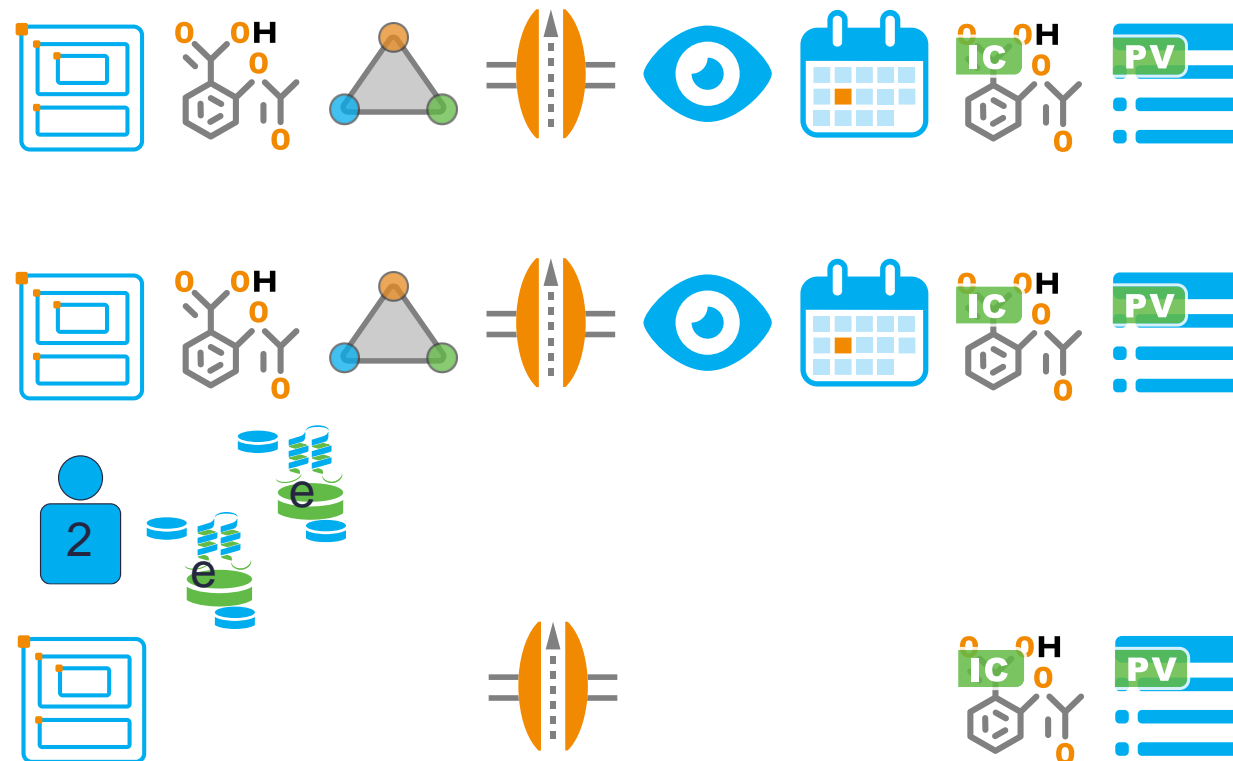


CompoundB

31 years old female  
Extensive metabolizer



Pregnancy





# Project organization

Examples of combination

PKSIM

CompoundA

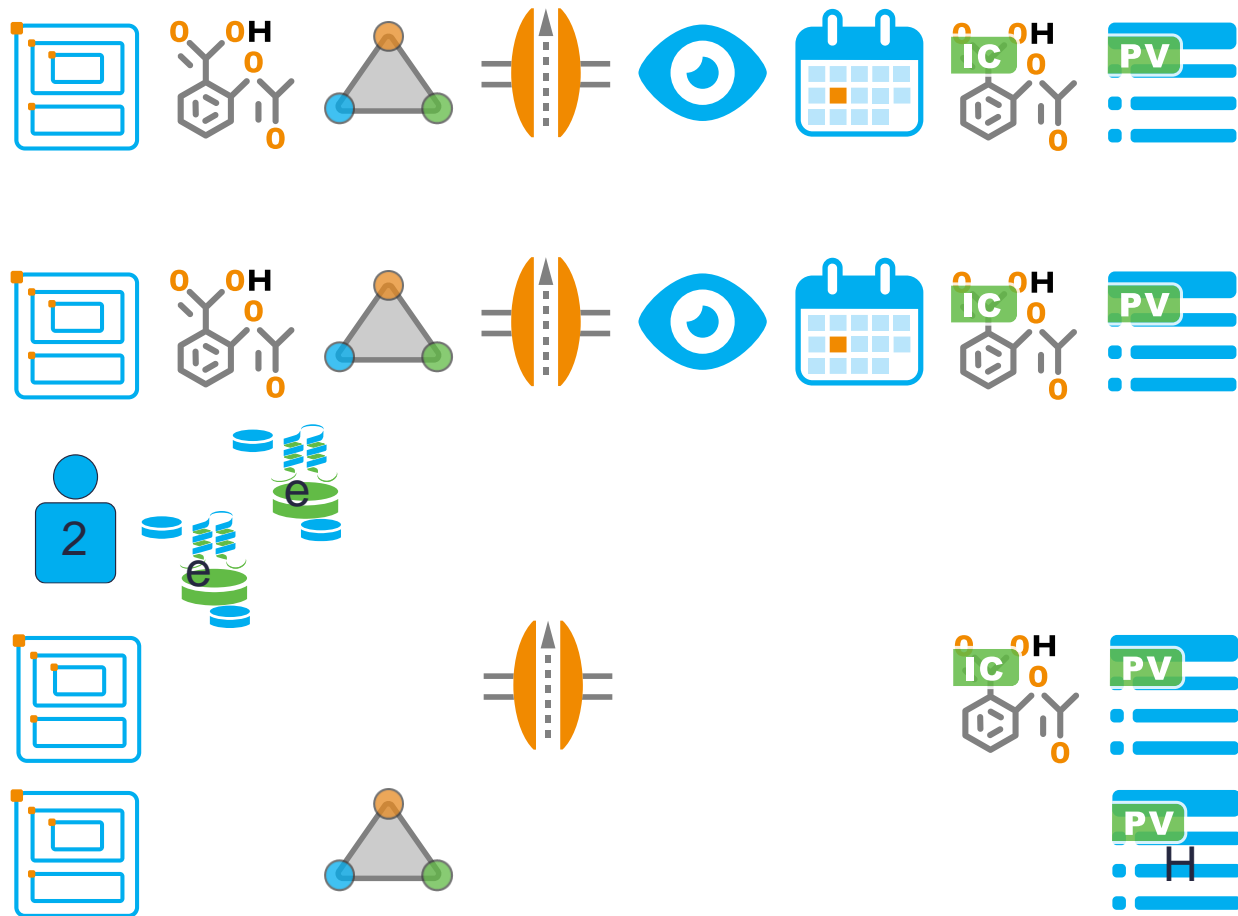
PKSIM

CompoundB

31 years old female  
Extensive metabolizer

Pregnancy

CompoundA effect model  
Healthy population





# Project organization

Examples of combination

PKSIM

CompoundA

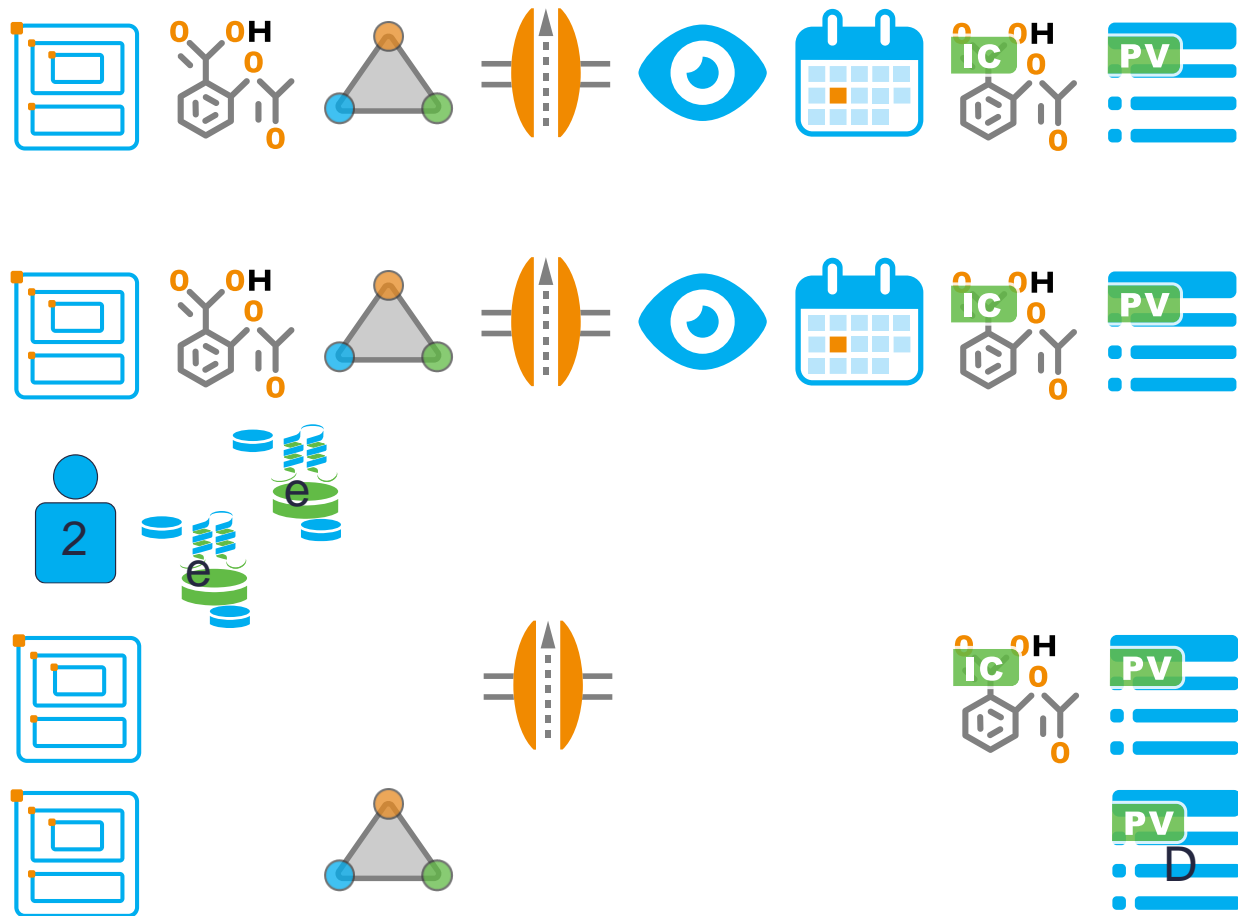
PKSIM

CompoundB

31 years old female  
Extensive metabolizer

Pregnancy

CompoundA effect model  
Disease population



# Use case

- Pregnancy model



# Use case – pregnancy model

- How to implement pregnancy as a module?
- Based on PBPK model by Dallmann et al.  
<https://github.com/Open-Systems-Pharmacology/Pregnancy-Models>
- Goal: a module that can be used with any PBPK model with minimal changes!



# Human pregnancy module

- General approach – implement all changes as separate modules, not within the PK-Sim modules
- Add new structures (e.g., organs) or overwrite existing structures (e.g., volume parameters of organs)
- Increasing complexity can be implemented as modules building upon each other

# Human pregnancy module


The here presented modules are available on GitHub!

[https://github.com/PavelBal/Pregnancy-Models/tree/v12\\_Modules](https://github.com/PavelBal/Pregnancy-Models/tree/v12_Modules)

This branch is 1 commit ahead of `Open-Systems-Pharmacology/Pregnancy-Models:master` .

Contribute







Sync fork

 **PavelBal**



Added pregnancy modules

1a9dce6 · 1 minute ago

56 Commits

 CotyledonPerfusionModel	Adds in silico cotyledon perfusion model and updates READ...	3 years ago
 Models	Adds acetaminophen pkml files	3 years ago
 Modules	Added pregnancy modules	1 minute ago
 ModelStructure.png	Corrected figure	3 years ago
 MoleculeBB_FetalFractionUnbound.png	Updated README	3 years ago
 README.md	Added pregnancy modules	1 minute ago

README

## Experimental module-based implementation for OSPS version 12

This branch contains an experimental implementation of the pregnancy model as extension modules utilizing the modularization concept implemented in Version 12 of the OSP software. As the software is still in development, this implementation cannot be considered as a final one.

## Physiologically Based Pharmacokinetic Models for

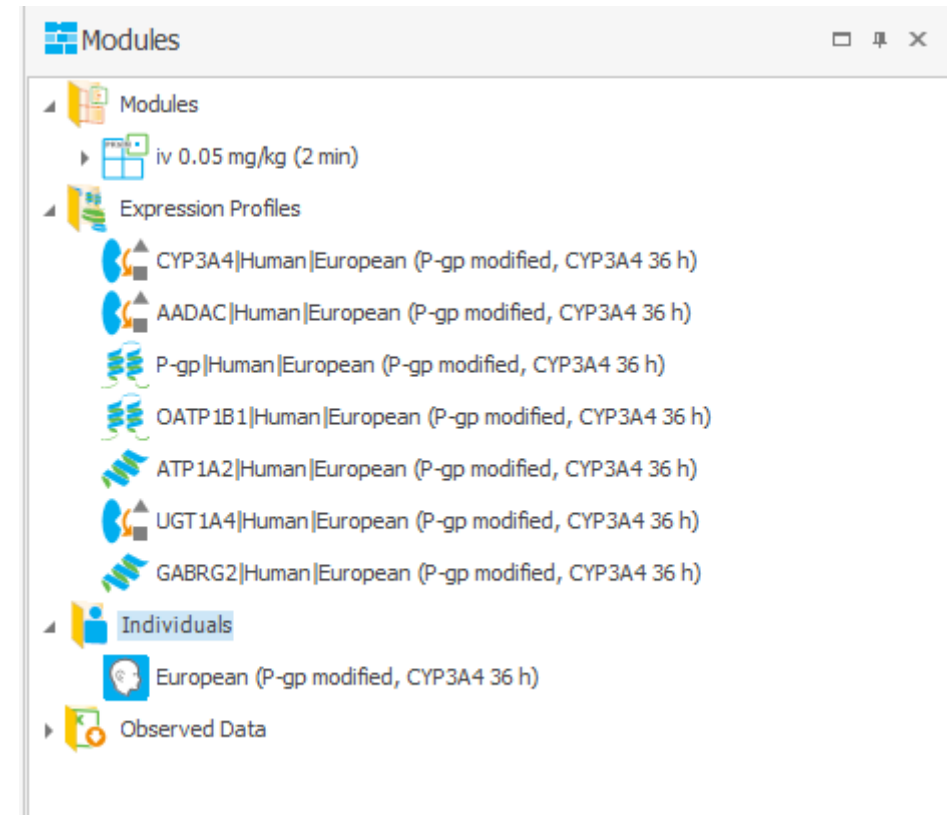




# Human pregnancy module

Extending a PBPK model

1. Develop a PBPK model in PK-Sim (example – Midazolam)
2. Send the model to PK-Sim





# Human pregnancy module

Extending a PBPK model

1. Develop a PBPK model in PK-Sim (example)
2. Send the model to PK-Sim
3. Create a pregnant individual

The screenshot shows the 'Create Individual' dialog box in PK-Sim. The 'Name' field is set to 'Pregnant'. The 'Biometrics' tab is selected, and the 'Anatomy & Physiology' sub-tab is active. The 'Population Properties' section includes dropdowns for 'Species' (Human), 'Population' (Pregnant (Dallmann et al. 2017)), and 'Gender' (Female). The 'Calculation methods' section has two rows: 'Endothelial surface areas' and 'Body surface area' on the left, and 'Organ vascularization' and 'Mosteller' on the right. The 'Individual Parameters' section contains input fields for 'Age' (30.00, year(s)), 'Weight' (60.00, kg), 'Height' (163.00, cm), and 'BMI' (22.58, kg/m²). A 'Value origin' field is also present. A 'Mean' button is located to the right of the parameter fields. At the bottom, there are navigation buttons: 'Previous', 'Next', 'OK', and 'Cancel'.



# Human pregnancy module

Extending a PBPK model

1. Develop a PBPK model in PK-Sim (example – Midazolam)
2. Send the model to PK-Sim
3. Create a pregnant individual
4. Load the pregnancy modules



# Human pregnancy module

Extending a PBPK model

1. Develop a PBPK model
2. Send the model to
3. Create a pregnant
4. Load the pregnant

Spatial Structure: Human Pregnancy Maternal - Organism

Parameters Formulas

Tree Diagram Properties Parameters

Organism: ☒ Show advanced parameters ☐ Group parameters

Name	Value	Value Origin	Dimension	Favorites	
Hematocrit	<NaN>		Dimensionle...	<input type="checkbox"/>	X
Hematocrit Table	0.41		Dimensionle...	<input type="checkbox"/>	X
Maternal Age	<NaN>		Time	<input type="checkbox"/>	X
MeanBW	<NaN>		Mass	<input type="checkbox"/>	X
MeanBW Table	60.00 kg		Mass	<input type="checkbox"/>	X
Volume (plasma)	<NaN>		Volume	<input type="checkbox"/>	X
Weight	<NaN>	? Unknown	Mass	<input type="checkbox"/>	X
Weight of blood organs	<NaN>		Mass	<input type="checkbox"/>	X
Weight of tissue organs	<NaN>		Mass	<input type="checkbox"/>	X
Weight_maternal	<NaN>		Mass	<input type="checkbox"/>	X

Tree structure:

- ★ Favorites
- ✎ User Defined
- MoleculeProperties
  - Organism
    - MoleculeProperties
      - ArterialBlood
      - Brain
      - Breasts
      - Endometrium
      - Fat
      - Heart
      - Kidney
      - Lung
      - Myometrium
      - PlacentaFetal
      - PlacentaMaternal
      - PortalVein
      - Skin
      - VenousBlood
    - Neighborhoods



# Human pregnancy module

## Extending a PBPK model

- 1. Develop
- 2. Send
- 3. Create
- 4. Load

Spatial Structure: Human Pregnancy Maternal - Organism

Parameters Formulas

Tree Diagram

Favorites

User Defined

MoleculeProperties

Organism

- ArterialBlood
- Brain
- Breasts
- Endometrium
- Fat
- Heart
- Kidney
- Lung
- Myometrium
- PlacentaFetal
- PlacentaMaternal
- PortalVein
- Skin
- VenousBlood

- Neighborhoods

Properties Parameters

ArterialBlood:

Show advanced parameters

Group parameters

Name	Value	Value Origin	Dimension	Favorites
Volume	<NaN>		Volume	
Volume Table	0.321		Volume	

Properties Tags

Name: Volume Table

Properties

Dimension: Volume

Group: MoBi

Value origin:

Favorite

Plot parameter

Advanced parameter

Can be varied in population

Value

Formula type: Table (multiple time discrete and piecewise constant numeric values)

Formula name: VOLUME\_martblood

Use derivative values

Time [h]	Y-Value []	Restart...
262980.00	0.32	
263436.02	0.32	
263508.02	0.32	
263652.02	0.33	

VOLUME\_martblood []

Time [h]

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# Human pregnancy module

Extending a PBPK model

1. Develop a PBPK model in PK-Sim (example – Midazolam)
2. Send the model to PK-Sim
3. Create a pregnant individual
4. Load the pregnancy modules
5. Extend the Initial Conditions



# Human pregnancy module

Extending a

- 1. Develop a
- 2. Send the
- 3. Create a
- 4. Load the
- 5. Extend th

Select a spatial structure and molecules

Spatial structure: Human Pregnancy Maternal - Organism

Molecules:

<input type="checkbox"/>	Molecule
<input checked="" type="checkbox"/>	iv 0.05 mg/kg (2 min) - Molecules
<input type="checkbox"/>	CYP3A4
<input type="checkbox"/>	AADAC
<input type="checkbox"/>	P-gp
<input type="checkbox"/>	OATP1B1
<input type="checkbox"/>	ATP1A2
<input type="checkbox"/>	UGT1A4
<input type="checkbox"/>	GABRG2
<input checked="" type="checkbox"/>	Midazolam
<input type="checkbox"/>	Midazolam-CYP3A4-Optimized Metabolite
<input type="checkbox"/>	Midazolam-UGT1A4-Optimized Metabolite
<input type="checkbox"/>	Midazolam-GABRG2-Buhr 1997 Complex

The building block will be extended with new values for selected *molecules* in all physical containers in the selected *spatial structure*

OK ☒ Cancel ☒





# Human pregnancy module

Extending a PBPK model

1. Develop a PBPK model in PK-Sim (example – Midazolam)
2. Send the model to PK-Sim
3. Create a pregnant individual
4. Load the pregnancy modules
5. Extend the Initial Conditions
6. Create a pregnant simulation

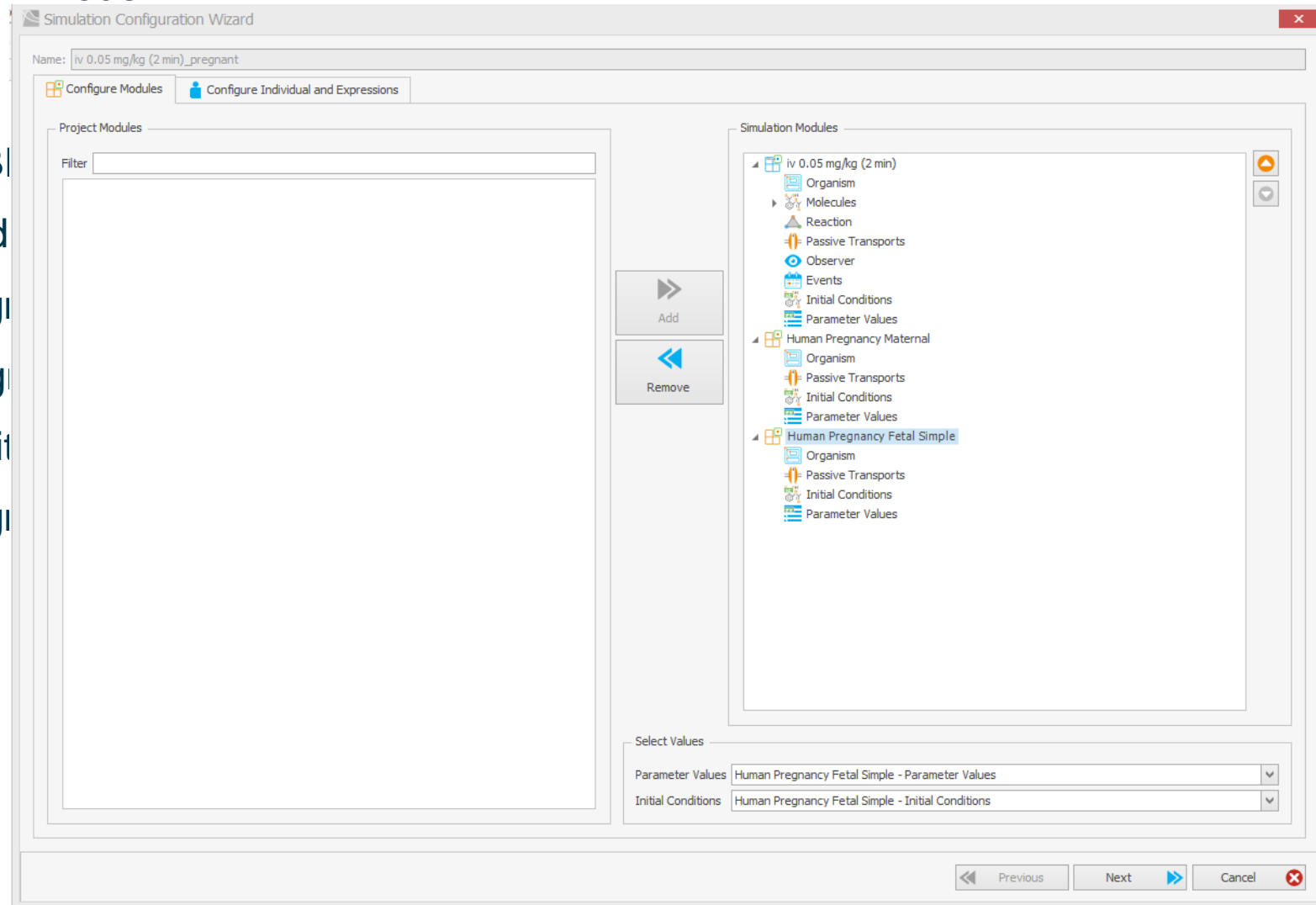




# Human pregnancy module

## Extending a PBPK model

1. Develop a PBPK model
2. Send the model to the wizard
3. Create a pregnancy module
4. Load the pregnancy module
5. Extend the Initial Conditions
6. Create a pregnancy module

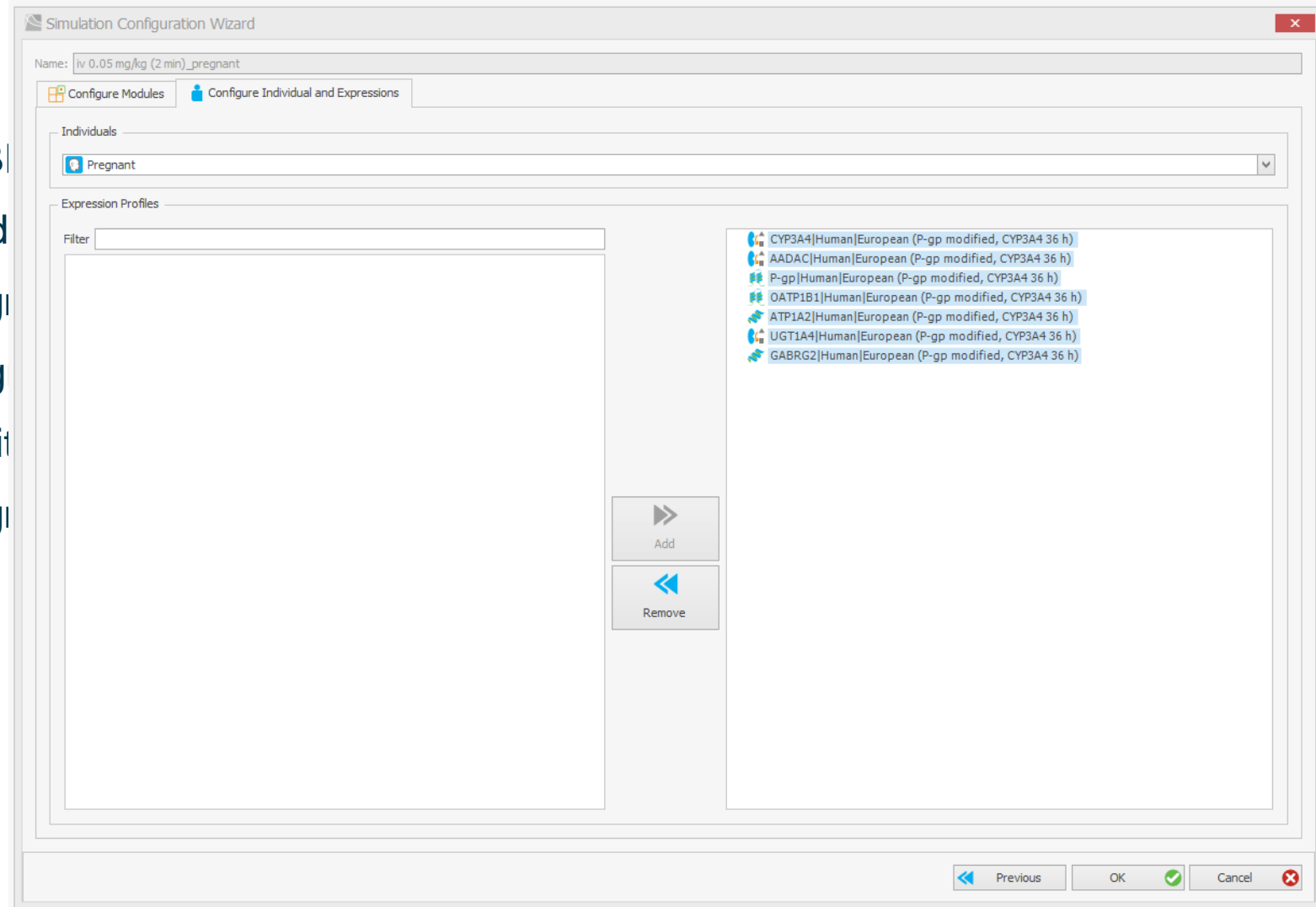




# Human pregnancy module

## Extending a PBPK model

1. Develop a PB
2. Send the mod
3. Create a pregn
4. Load the pregn
5. Extend the Ini
6. Create a pregn





# Human pregnancy module

Extending a PBPK model

1. Develop a PBPK model in PK-Sim (example – Midazolam)
2. Send the model to PK-Sim
3. Create a pregnant individual
4. Load the pregnancy modules
5. Extend the Initial Conditions
6. Create a pregnant simulation
7. Simulate!

# 03

## QSP model qualification

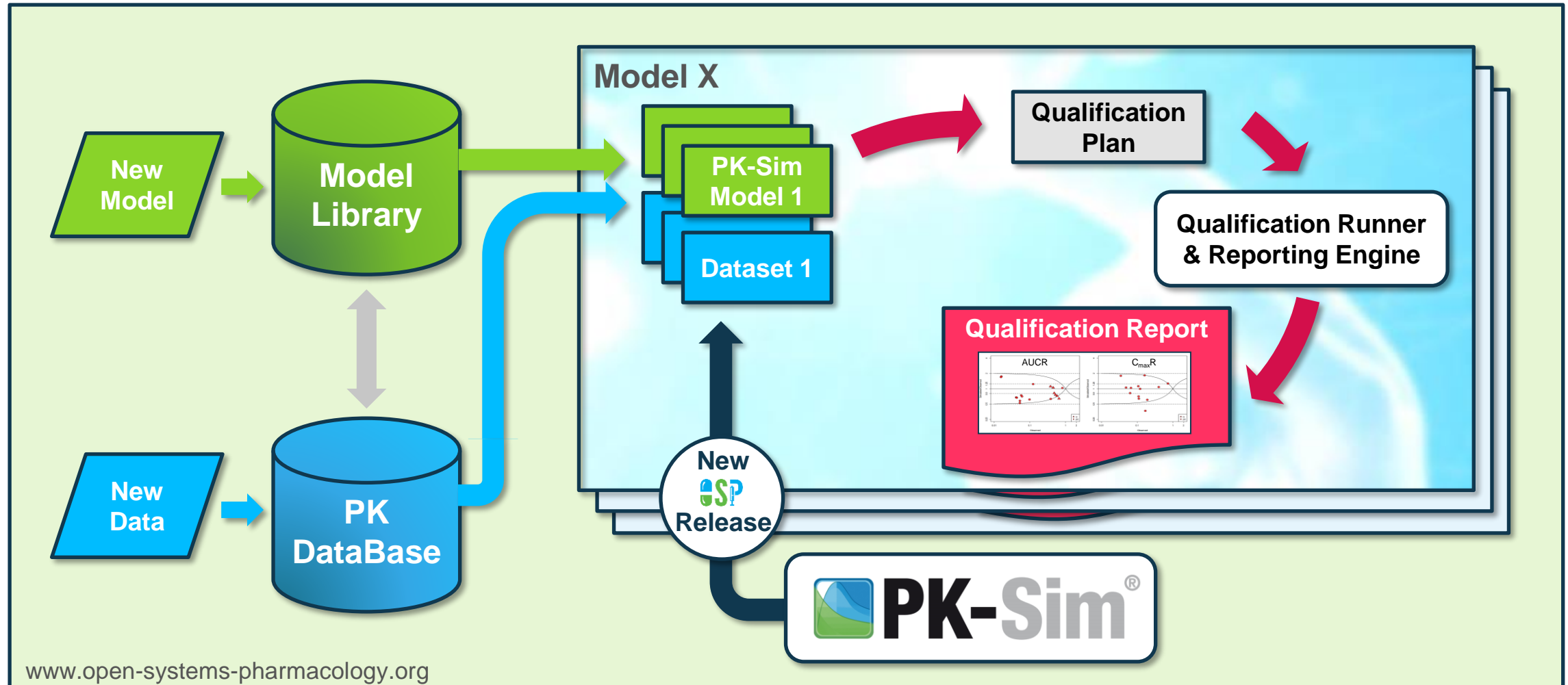
Outlook





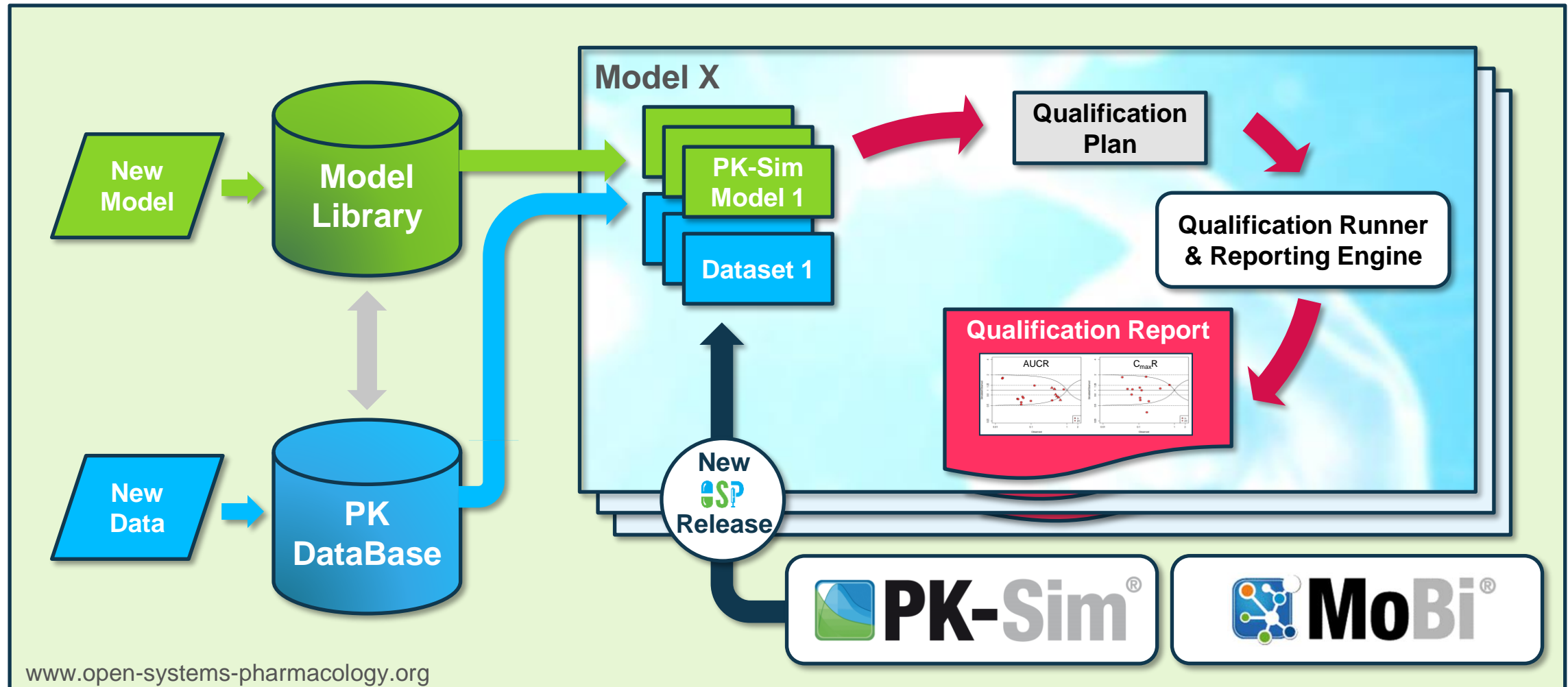
# Platform Qualification: Automatic (Re)-qualification Workflow

Sustainable and Agile (Re)-Qualification of Intended Use Scenarios for Regulatory Submissions



# Platform Qualification: Automatic (Re)-qualification Workflow

Sustainable and Agile (Re)-Qualification of Intended Use Scenarios for Regulatory Submissions



# Platform Qualification

## QSP model snapshot

- Key aspect is the **MoBi project snapshot**
  - PK-Sim modules snapshot(s)
  - Extension modules as pkml
  - Observed data
  - Model configurations & models
    - List of all user-defined (parameter) values
- RQ Workflow:
  - Re-create PK-Sim modules
  - Re-create model configurations & models
  - Apply user-defined values
  - Simulate and compare to observed data
  - Create Qualification Report



# 04

**Try v12 now!**



The first public beta of Version 12 has just been released!

Get it here:

[https://github.com/Open-Systems-  
Pharmacology/Suite/releases/tag/v12.0\\_beta1](https://github.com/Open-Systems-Pharmacology/Suite/releases/tag/v12.0_beta1)

## Getting started with OSMOSES:

<https://github.com/Open-Systems-Pharmacology/OSMOSES/blob/develop/Documentation/Getting%20Started.md>

# Thank you!

Pavel Balazki