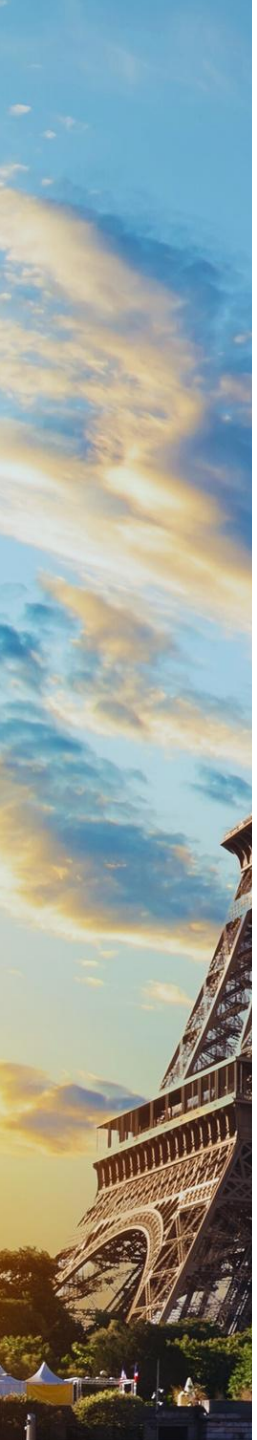

# Software Verification, Validation, and (CoU) Qualification of Open Source M&S Software

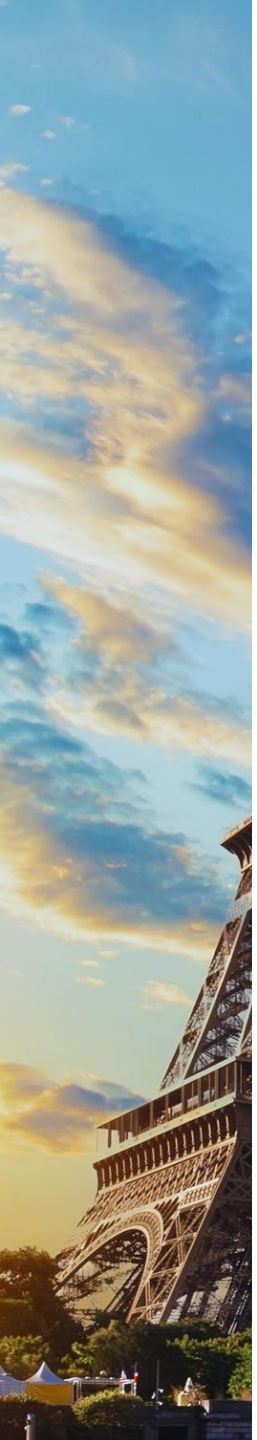
## for Regulatory Use in Translational Model-Informed Drug Development

Stephan Schaller, on behalf of the OSP Management Team
(Jörg Lippert, Rolf Burghaus, Ibrahim Ince, Andreas Kovar, Lars Küpfer, Thorsten Lehr, Stephan Schaller, Jan Schlender, Michaël Sevestre, Erik Sjögren, Juri Solodenko, Alexander Staab, and Donato Teutonico)



# Today's Journey:
## From Open Source to Regulatory Confidence

- The Challenge: Regulatory Qualification in MIDD
  Why mechanistic models need robust verification & validation
- Transparent Infrastructure: GitHub Ecosystem
  How open source enables continuous validation & community review
- OSP's Three Pillars of Trust
  Software Validation • CoU Qualification • Installation Verification
- Qualification in Action: Real-World Applications
  DDI, pediatrics, special populations - aligned with EMA/FDA frameworks
- Beyond PBPK: The Modular MIDD Future
  Expanding to PBPK-QSP integration and qualification for complex translational models



# Disclosure & Acknowledgements

- **Stephan Schaller is a member of the OSP Management Team**
  (Jörg Lippert, Rolf Burghaus, Ibrahim Ince, Andreas Kovar, Lars Küpfer, Thorsten Lehr, Stephan Schaller, Jan Schlender, Michaël Sevestre, Erik Sjögren, Juri Solodenko, Alexander Staab, and Donato Teutonico)
- This presentation has been prepared for the “EMA multi-stakeholder workshop on reporting and qualification of mechanistic models for regulatory assessment (8 – 9 October 2025)”
- Acknowledging the Contributions of
  - Juri Solodenko (Software Verification & Validation)
  - OSP MT/Community/Publications: Other Content

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# The Challenge: Regulatory Qualification in MIDD

## Why mechanistic models need robust verification & validation

# Requirements of Mechanistic Model-based Assessment in a Regulatory Context

## TRACEABLE

Models allow traceability of data, assumptions, and parameters across molecules (and species).

## ACCESSIBLE

Open-access, shared libraries, ensuring equitable access and trust

## MECHANISTIC

Enabling confidence in knowledge-based extrapolation across data gaps

## REPRODUCIBLE

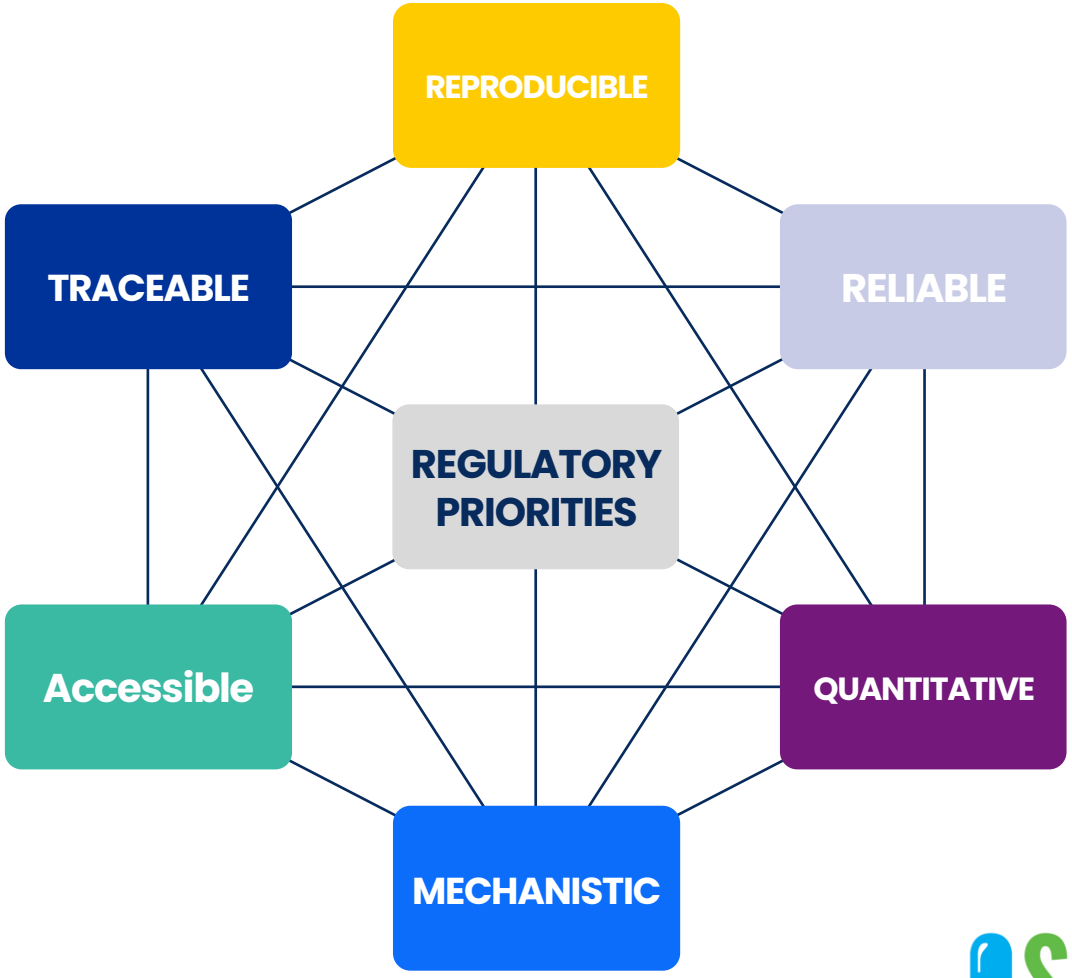
Transparent, reproducible predictions strengthen regulatory confidence.

## RELIABLE

Continuous validation, automated testing and multi-institutional verification

## QUANTITATIVE

Support quantitative, human-relevant decision making.



# The Regulatory Challenge

## Mechanistic models are pivotal but face qualification hurdles

### The Qualification Paradox

**The Promise**

- Mechanistic models are pivotal for MIDD
- FDA & EMA guidances endorse PBPK/QSP use
- Regulatory decisions increasingly model-informed

✓ Growing acceptance

**The Reality**

- No universal qualification framework established
- Platform performance verification unclear
- Version control & lifecycle management complex
- Transparency requirements challenging

⚠ Implementation barriers

# The Regulatory Challenge

## Mechanistic models are pivotal but face qualification hurdles

### The Key Hurdle (Partially Solved for PBPK)

- • **Evidence Package:**
  Series of successful prospective predictions needed
  • **Full Transparency:**
  Processes, tools, and models must be auditable
  • **Technical Burden:**
  From scientific content to computerized system validation
  • **Resource Gap:**
  No single stakeholder can compile all requirements alone
- *"The EMA guideline's 'qualification for intended use' creates challenges that exceed any individual organization's capacity"*

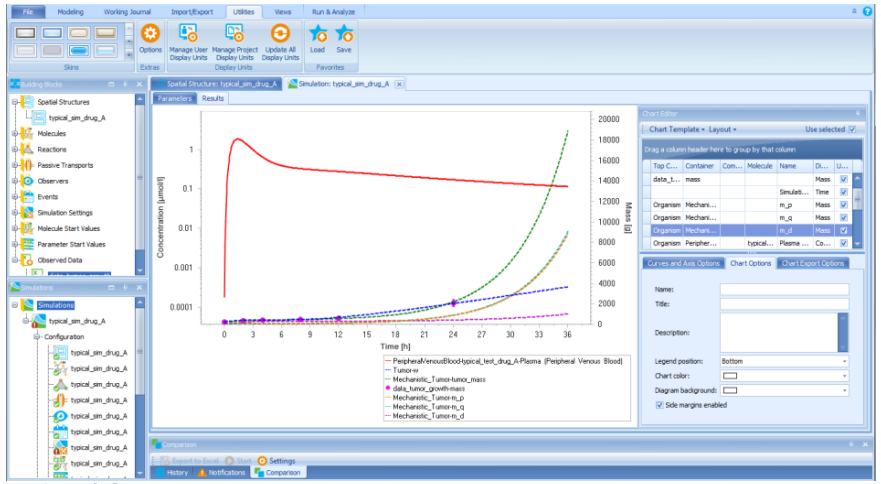

# Transparent Infrastructure: GitHub Ecosystem

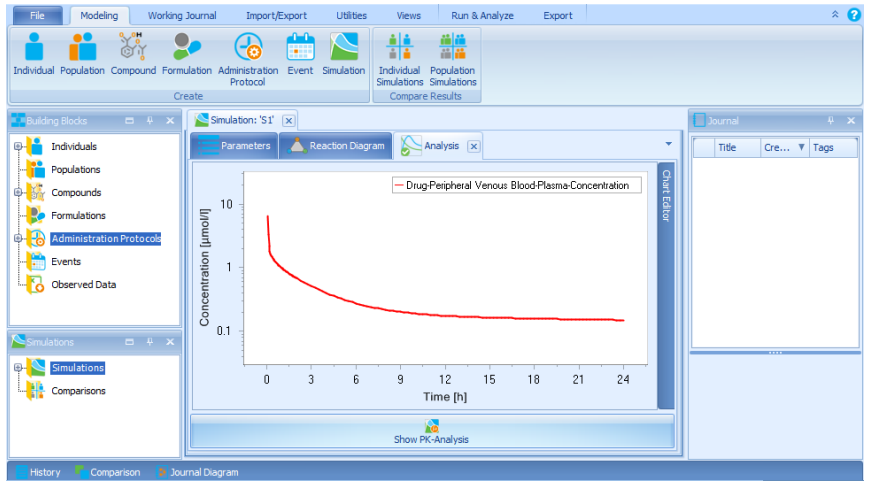
How open source enables continuous validation & community review

# Open Systems Pharmacology Suite: PK-Sim® & MoBi®:

- An open-source Multiscale Physiologically-Based & Mechanistic Modeling platform which has been developed and refined for **20 years**!

MoBi® & PK-Sim® = OPEN SYSTEMS PHARMACOLOGY





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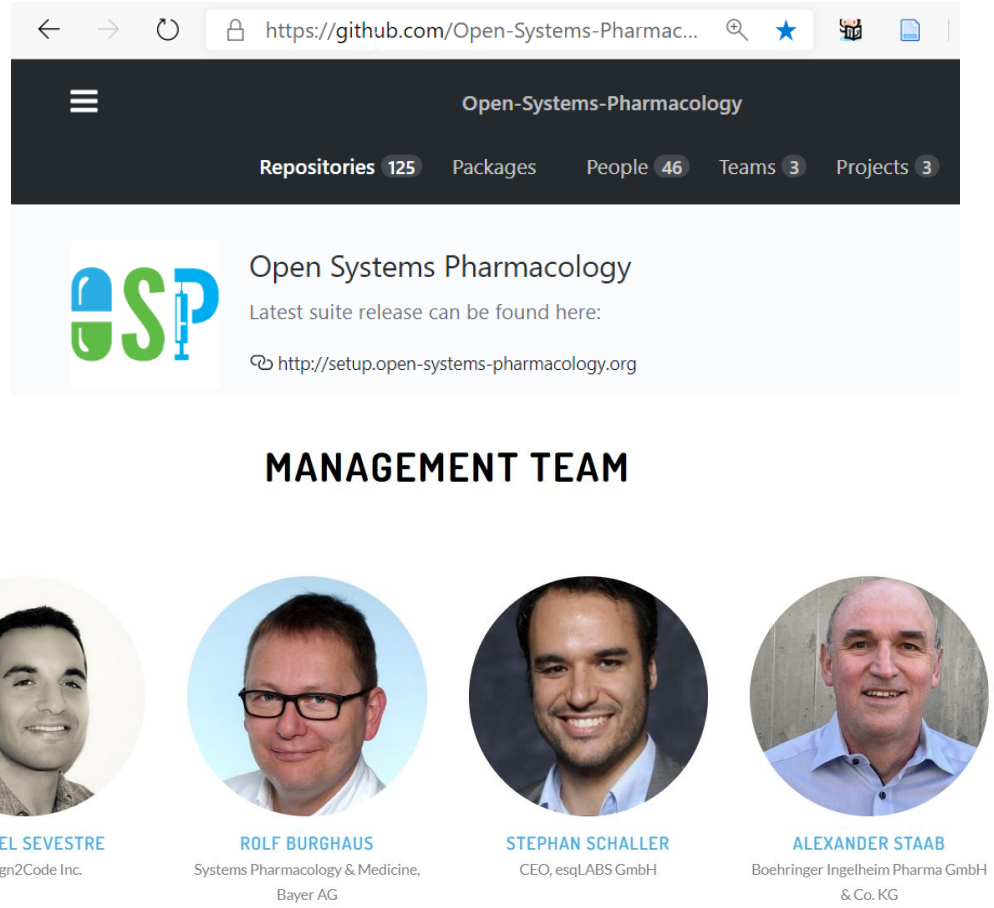
# The OSP's Philosophy on Openness
## Open Access, Open Source, and Open Science




Open Source since 2017 on GitHub

8+ releases, GPLv2 license

esqlabs
we empower life sciences
SANOFI
NOVARTIS
Boehringer Ingelheim
BAYER
DESIGN{2}CODE
UF UNIVERSITY of FLORIDA
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RWTH AACHEN UNIVERSITY
Pharmetheus
Pharmacometrics Consulting Services

http://www.open-systems-pharmacology.org/



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# The OSP's Philosophy on Openness
## Mission & Vision

# OSP Roadmap

## The OSP Roadmap builds on the Vision & Mission of Open Systems Pharmacology

### Vision

Robust and reliable, easy-to-use modeling & simulation tools, processes and models for pharmaceutical and other life-sciences applications qualified and accepted by a scientific community from academia, regulatory agencies and industry available and open to everyone.

### Mission

Provide a platform for joint development, review & qualification, and application of state-of-the-art tools for PBPK and Systems Pharmacology modeling and an open library of models for application as well as method & tool qualification purposes. Promote the idea of pre-competitive open collaboration for the advancement of modeling & simulation sciences in pharmaceutical and life science.

# The OSP's Philosophy on Openness

## Community-driven development model (Donations across components)

- DDI
- Special Populations
- Absorption
- PD
- Statistical modelling
- First in Human (IVIVE)
- Omics
- Suite Release Management
- Automation/Qualification
- Community Engagement (PR)
- Biologics
- Nonclinical PBPK
- PBBM
- HT PBPK

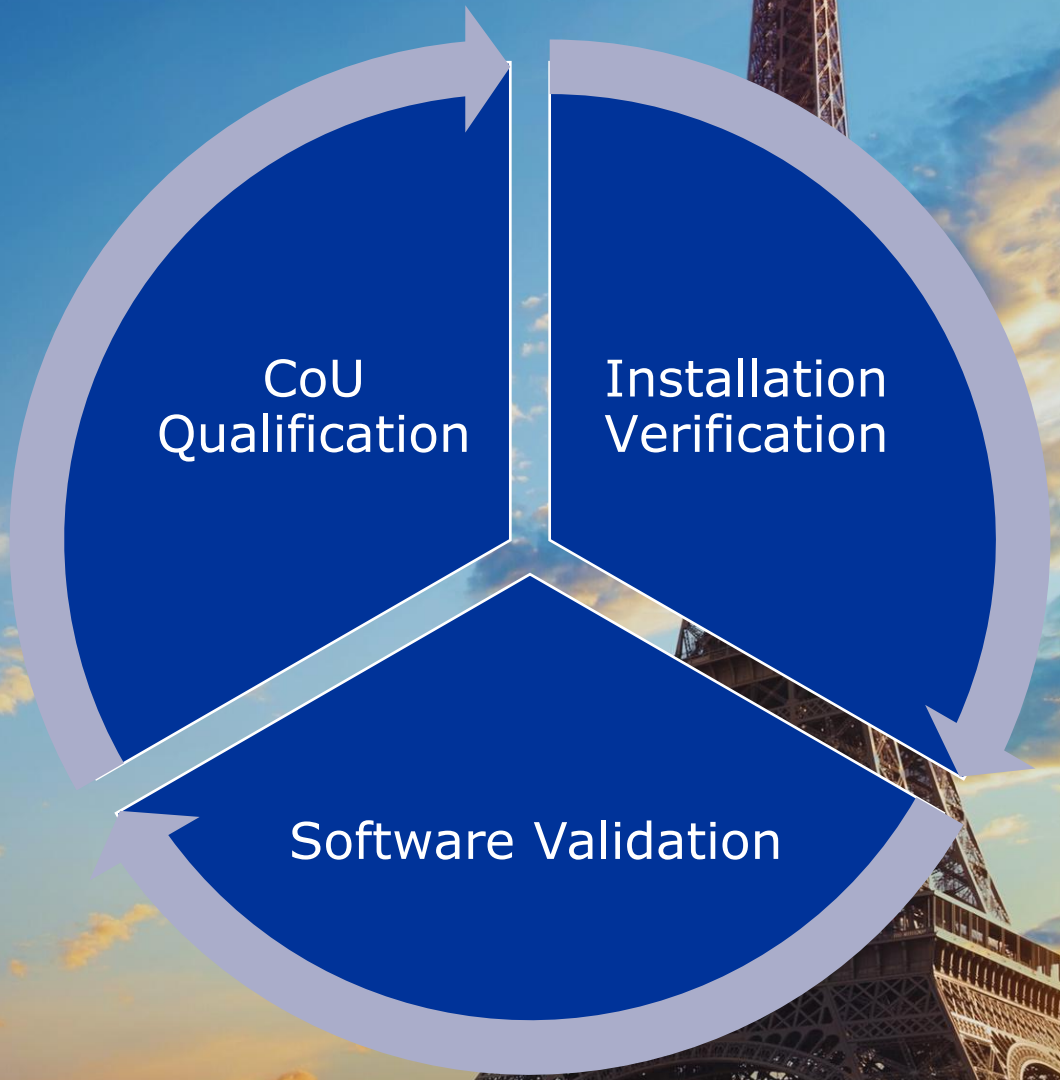
**Dedicated Focus Groups have been established to conceptualize, design and progress the individual areas, the Management Team will coordinate the interplay of focus areas and interfaces between them**

Focus groups shall be the owner of the development in the respective focus area, they are expected to conceptualize and coordinate activities of the respective field.

| | | |
|---|---|---|
| **DDI** | Quantitative DDI predictions (CYPs as well as transporters) are one of the key applications for PBPK and are a prerequisite for designing efficient clinical development programs and studies. A comprehensive library of well documented, qualified perpetrators and victims is a prerequisite for acceptance of DDI predictions from regulatory authorities. | Sebastian Frechen (@sfrechen) |
| **IVIVE** | • Improve and facilitate use of IVIVE in PK-Sim<br>• Provide guidelines on how to conduct IVIVE in PK-Sim<br>• Facilitate integration of in vitro data in prediction of DDI (e.g. integration of fraction metabolized)<br>• Extrapolation of Caco-2 permeabilities to effective permeabilities | Donato Teutonico (@teutonicod) |
| **Special populations** | The addition of new or updated virtual populations is required to expand the application scope of the software in a consistent manner across users. The overall objectives are to define a process for<br>1. technical generation of populations destined for the OSP Suite and,<br>2. evaluation of those populations.<br>This protocol will allow populations to be added more efficiently. | Andrea Edginton (@Aedginto) |
| **Statistical Modelling** | Statistical Modeling is a strategic theme of the OSP MT. Statistical modeling is a key enabler for PBPK and QSP M&S. Respective capabilities are required for all application areas to quantitatively assess population variability and uncertainty in prior knowledge and posterior results. | Christian Diedrich (@DiedrichC) |

# OSP's Three Pillars of Trust

- Software Validation
- CoU Qualification
- Installation Verification



# The OSP Suite Architecture: PK-Sim, MoBi & R components

## Import

Excel® CSV
NONMEM® SBML

## Export

Excel® CSV
PDF JSON

## Modeling Tools

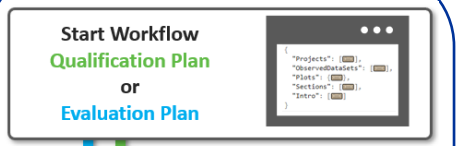
PK-Sim®
PBPK modeling & simulation

MoBi®
(PB)QSP modeling & simulation

Project snapshots (**JSON**)

OSP Model exchange format (**PKML**)

## Qualification Framework




Qualification Runner & Reporting Engine


## R packages

- Reporting Engine
- Plot-Library (TLF)
- Parameter Identification

…

## OSP Interfaces

**R** (statistical computing)

## Validation/Automation Tools

- Installation Validator
- Command Line Interface (CLI)

…

**PBPK**: Physiologically based pharmacokinetic
**(PB)QSP**: (Physiologically based) Quantitative systems pharmacology

**TLF**: Tables, listings and figures

# Quality Assurance of the OSP Suite
## Continuous Software Validation & Qualification

*OSP Suite is an open-source platform that is developed in a fully transparent manner on **GitHub** (the largest hosting platform for open-source software).*

Two main steps are used to ensure the quality of the OSP Suite: **Validation** and **Qualification.**

- **Platform Validation**: refers to the process of confirming that the PBPK software platform accurately represents the mathematical models and algorithms it is intended to implement.

  This includes verifying that the software correctly performs the calculations and simulations based on the underlying physiological and pharmacokinetic principles.

- **Platform Qualification** for intended use: involves demonstrating that the PBPK software platform is suitable for the specific research or regulatory purpose for which it is intended.

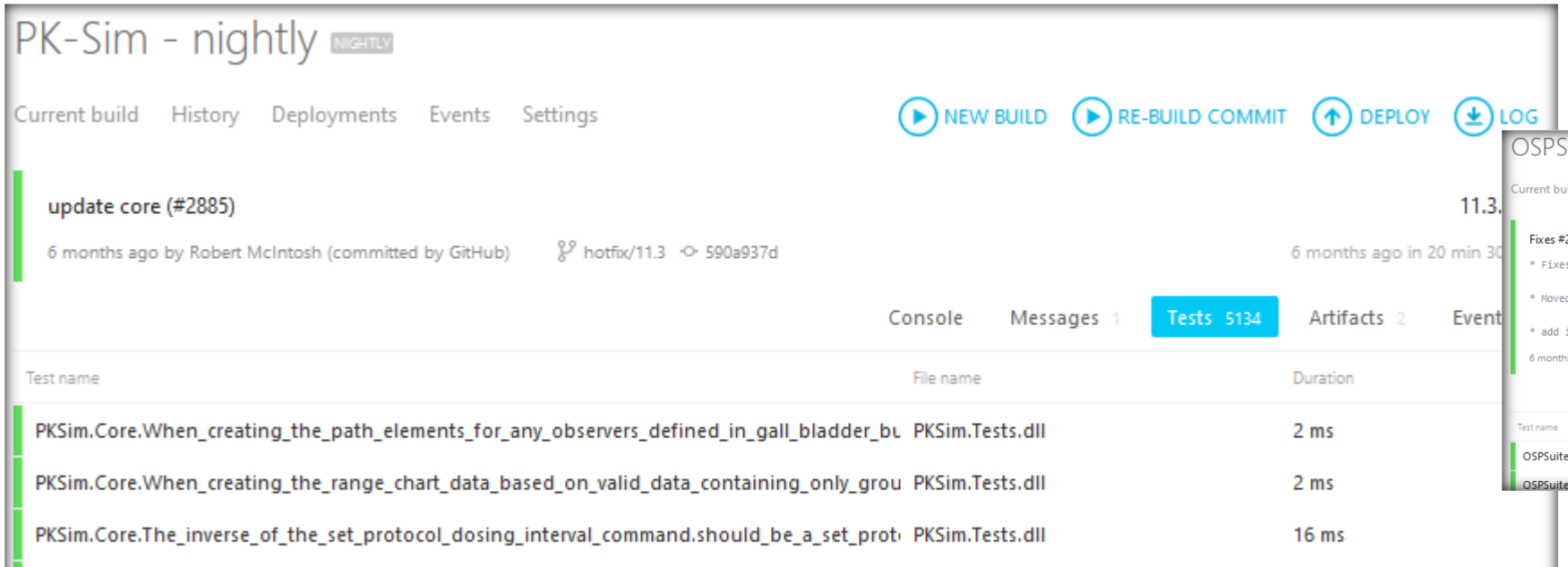
  This goes beyond general validation and includes assessments of the platform's features, functionalities and performance metrics in the context of specific use cases.

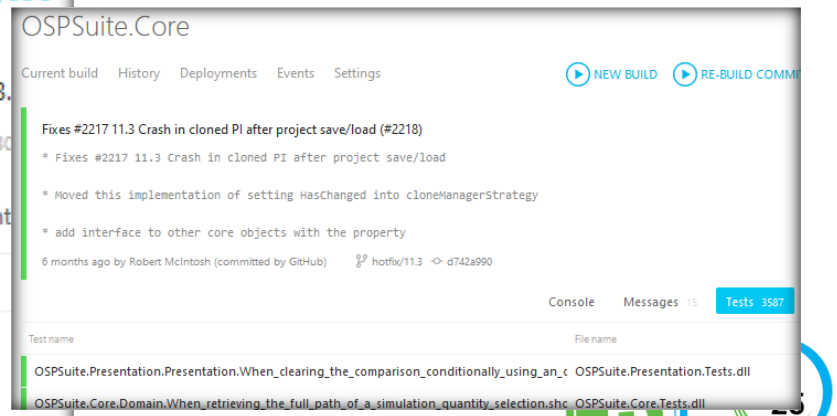
  For example, if a platform is intended to predict drug-drug interactions, qualification would include demonstrating that it can accurately model and predict these interactions for a range of compounds.

# Continuous Software Validation

## A growing, extensive library of test cases tested with validated programs

1. Automated testing of the correct behavior of software modules.
   - Tests (unit tests, integration tests...) are triggered with every software build (e.g. about 11600 automated tests for the 11.3 release).
   - New changes are integrated only if all tests are passed.
   - Full test logs for every software build and release are documented on GitHub and available for anyone to view.



# Continuous Software Validation

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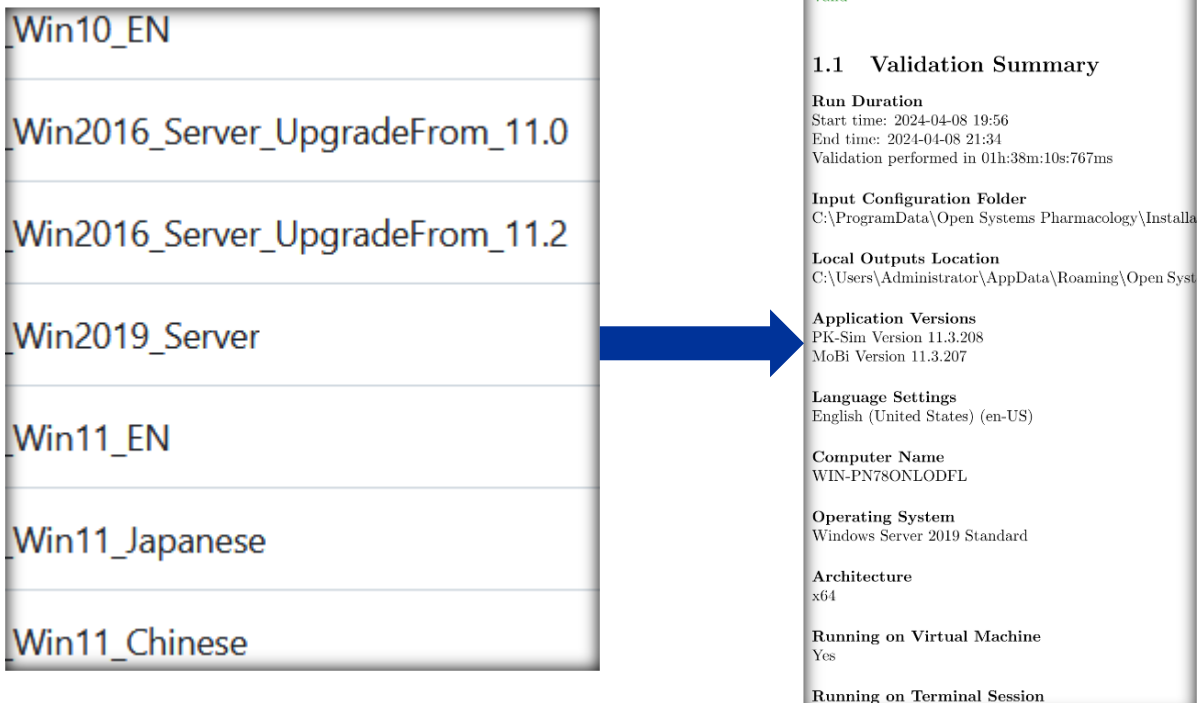
1. Automated testing of the correct behavior of software modules.
2. Automated comparison of simulation results between software versions for specific combinations of compounds, organisms, calculation methods and model options..

| | File | Modell | Simulations | | Individual | | | | | | | Compound | | | | | Application | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | | | 155 | Params | Population | Gender | Age | Aging | Enzymes | Transp. | Bind. | Type | pKa | Partition | Permeab. | Process | Dosing | Type | Formulation |
| 43 | Human_SingleORAL_Weibull_AsSuspention | 4Comp | 3 | fu/MW/Lipo | ICRP_2002 | MALE | 30 | --- | --- | --- | --- | small | Acid | RR | Standard | | Single | Oral | Weibull |
| 44 | Human_UncompetitiveInhibition | 4Comp | | --- | ICRP_2002 | MALE | 30 | | CYP3A4 | | | small | Acid | RR | Standard | Specific_MM CYP3A4 | DI_12_12 | IntravenousBolus | |
| 45 | | | 1 | --- | | | | --- | | --- | --- | small | Acid | RR | Standard | UncompetitiveInhibition CYP3A4 | DI_6_6_6_6 | IntravenousBolus | |
| 46 | Minipig_SingleORAL_Dissolved | 4Comp | 3 | fu/MW/Lipo | Minipig | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | Single | Oral | Dissolved |
| 47 | Monkey_SingleORAL_Dissolved | 4Comp | 3 | fu/MW/Lipo | Monkey | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | Single | Oral | Dissolved |
| 48 | Mouse_SingleORAL_Dissolved | 4Comp | 3 | fu/MW/Lipo | Mouse | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | Single | Oral | Dissolved |
| 49 | Preterm_SingleIV_Age_0_GA_32_CYP3A4 | 4Comp | 1 | --- | Preterm | MALE | 0 | X | CYP3A4 | --- | --- | small | Acid | RR | Standard | 1stOrder CYP3A4 | Single | IntravenousBolus | |
| 50 | Preterm_SingleIV_Age_0_GA_32_GFR | 4Comp | 1 | --- | Preterm | MALE | 0 | X | --- | --- | --- | small | Acid | RR | Standard | GFR | Single | Intravenou | Dissolved |
| 51 | Preterm_SingleIV_Age_15_GA_32_CYP3A4 | 4Comp | 1 | --- | Preterm | MALE | 0,25 | X | CYP3A4 | --- | --- | small | Acid | RR | Standard | 1stOrder CYP3A4 | Single | IntravenousBolus | |
| 52 | Preterm_SingleIV_Age_15_GA_32_GFR | 4Comp | 1 | --- | Preterm | MALE | 0,25 | X | --- | --- | --- | small | Acid | RR | Standard | GFR | Single | Intravenou | Dissolved |
| 53 | Rabbit_SingleORAL_Dissolved | 4Comp | 3 | fu/MW/Lipo | Rabbit | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | Single | Oral | Dissolved |
| 54 | Rat_MultiORAL_6_6_6_6_Dissolved | 4Comp | 1 | --- | Rat | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | DI_6_6_6_6 | Oral | Dissolved |
| 55 | Rat_MultiORAL_6_6_12_Dissolved | 4Comp | 1 | --- | Rat | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | DI_6_6_12 | Oral | Dissolved |
| 56 | Rat_MultiORAL_8_8_8_Dissolved | 4Comp | 1 | --- | Rat | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | DI_8_8_8 | Oral | Dissolved |
| 57 | SingleIV_2Pores_Human | TwoPores | 4 | Kd (FcRn)_endo C_FcRn_endo(0) | ICRP_2002 | MALE | 30 | --- | --- | --- | --- | Large | Acid | Standard | Standard | | Single | IntravenousBolus | |
| 58 | SingleIV_2Pores_Monkey | TwoPores | 3 | Kd (FcRn)_endo C_FcRn_endo(0) | Monkey | --- | --- | --- | --- | --- | --- | Large | Acid | Standard | Standard | | Single | IntravenousBolus | |
| 59 | SingleIV_2Pores_Mouse | TwoPores | 4 | Kd (FcRn)_endo C_FcRn_endo(0) | Mouse | --- | --- | --- | --- | --- | --- | Large | Acid | Standard | Standard | | Single | IntravenousBolus | |
| | SingleIV_C1_4Comp | | | | | | | | | | | | | | | | | | |

# Continuous Software Validation

## A growing, extensive library of test cases tested with validated programs

1. Automated testing of the correct behavior of software modules.
2. Automated comparison of simulation results between software versions for specific combinations of compounds, organisms, calculation methods and model options.
3. Automated testing in different software environments (different operating systems, etc.).



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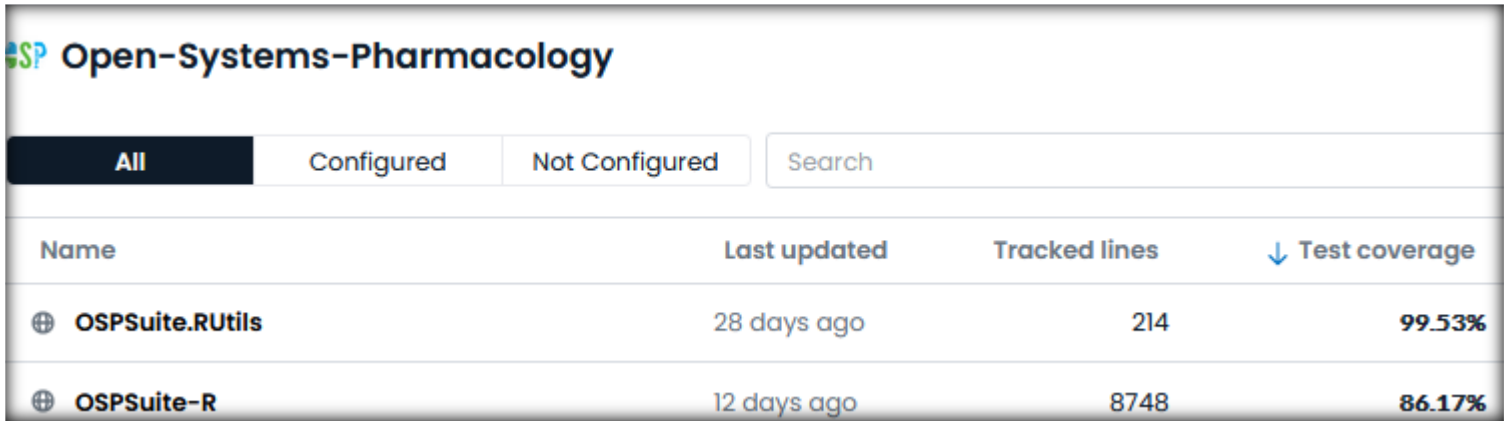
4. Automated code quality analysis (e.g. static code analysis, test coverage).



# Continuous Software Validation

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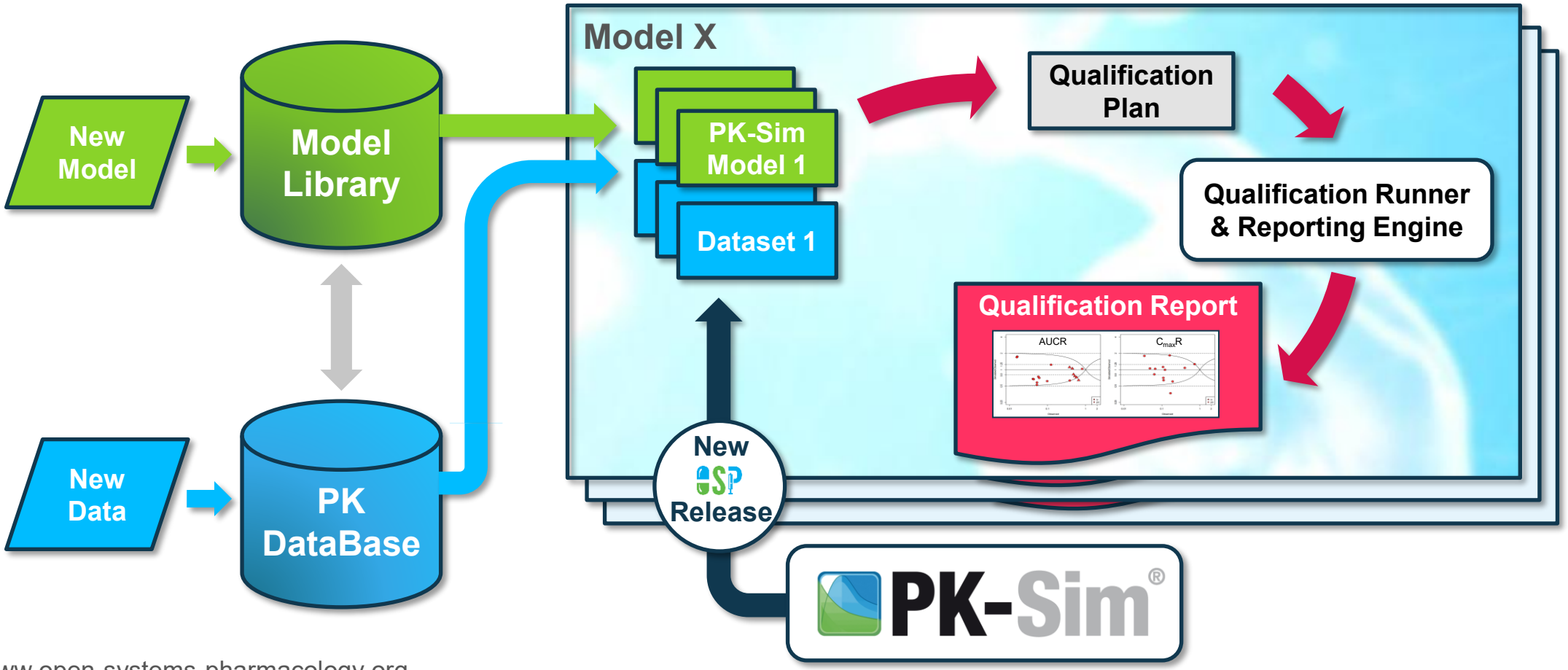
1. Automated testing of the correct behavior of software modules.
2. Automated comparison of simulation results between software versions for specific combinations of compounds, organisms, calculation methods and model options.
3. Automated testing in different software environments (different operating systems, etc.).
4. Automated code quality analysis (e.g. static code analysis, test coverage).
5. (Manual) testing of new features by scientific experts.

# Community-Driven CoU Qualification Framework
## Automatic (Re)-qualification Workflow

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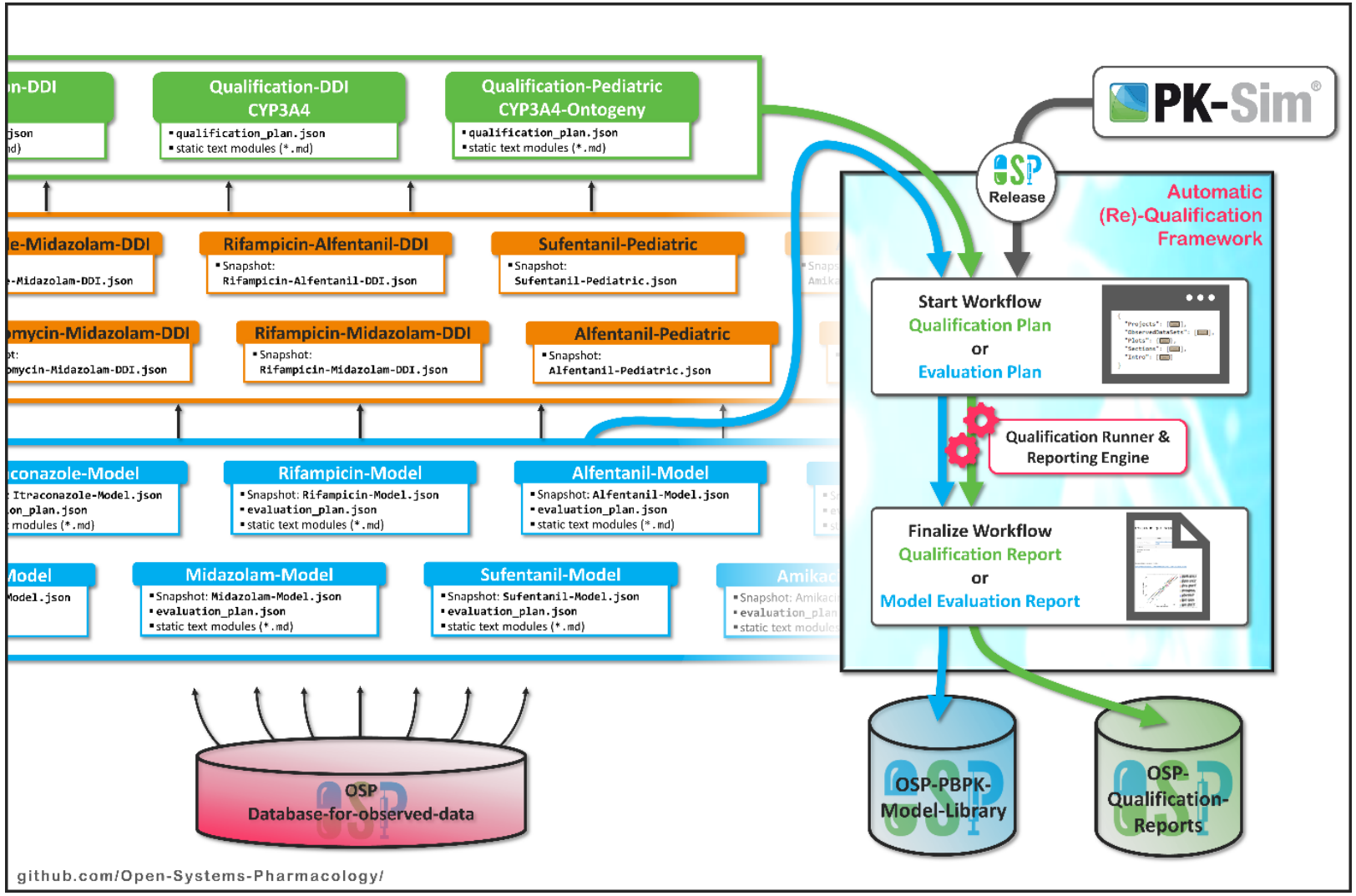
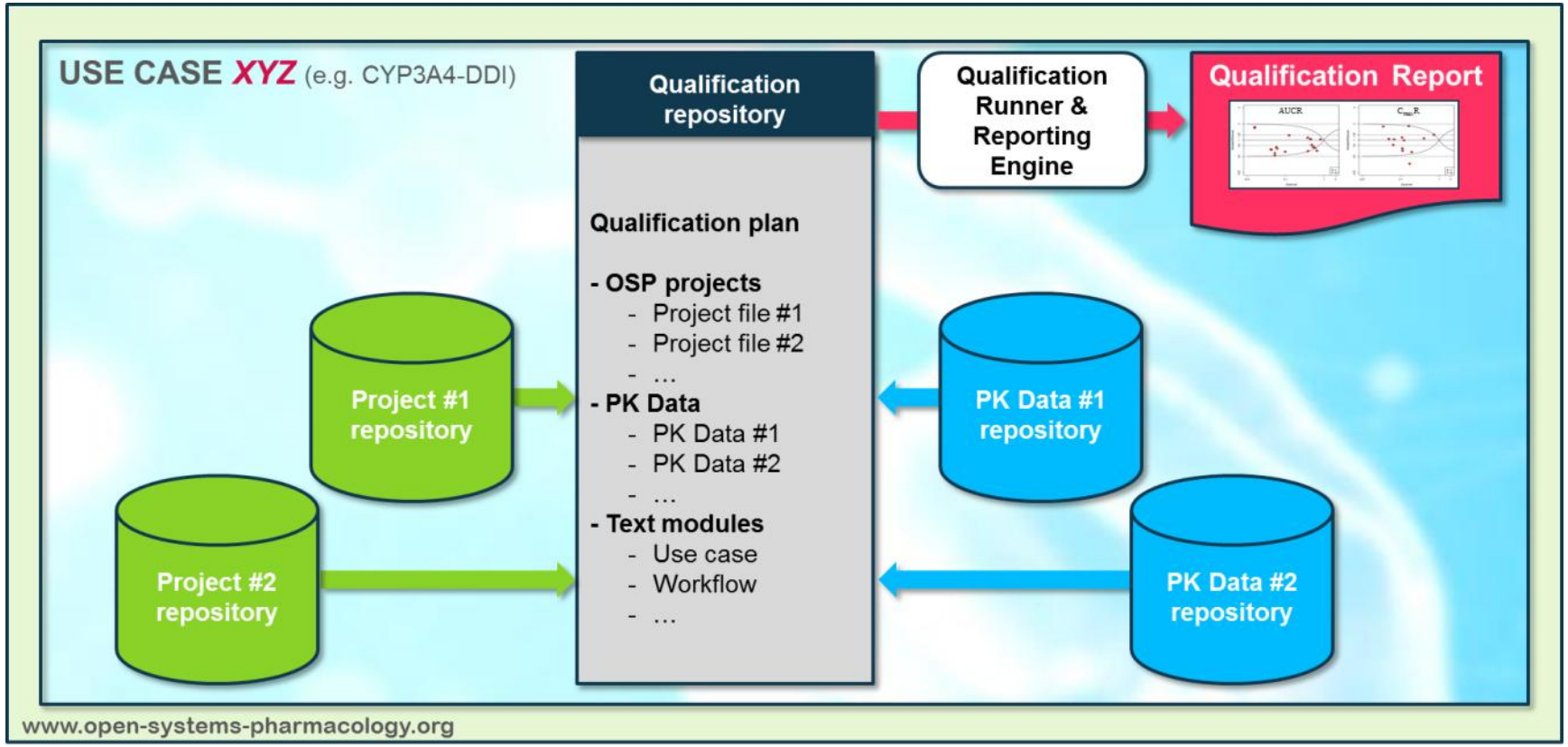
# Community-Driven CoU Qualification Framework
## Qualification Repository Structure

- Repository landscape with the embedded qualification framework.
- Various input repositories:
  - Blue: model repositories for single PBPK substance models (including a snapshot file and an evaluation plan),
  - Orange: dependent (intermediate) model repositories needed for specific qualification scenarios (including a snapshot file for specific simulation set-up),
  - Green: qualification repositories for specific qualification purposes, pink container
- The framework extracts PK data from the hosted database

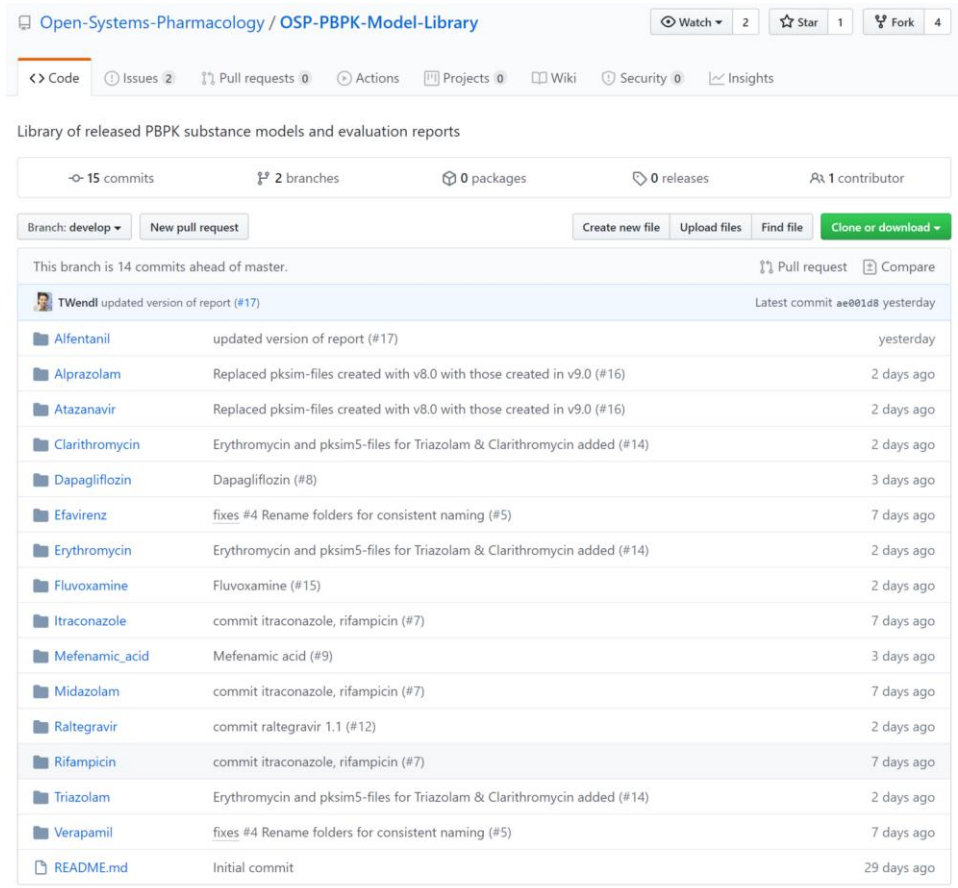


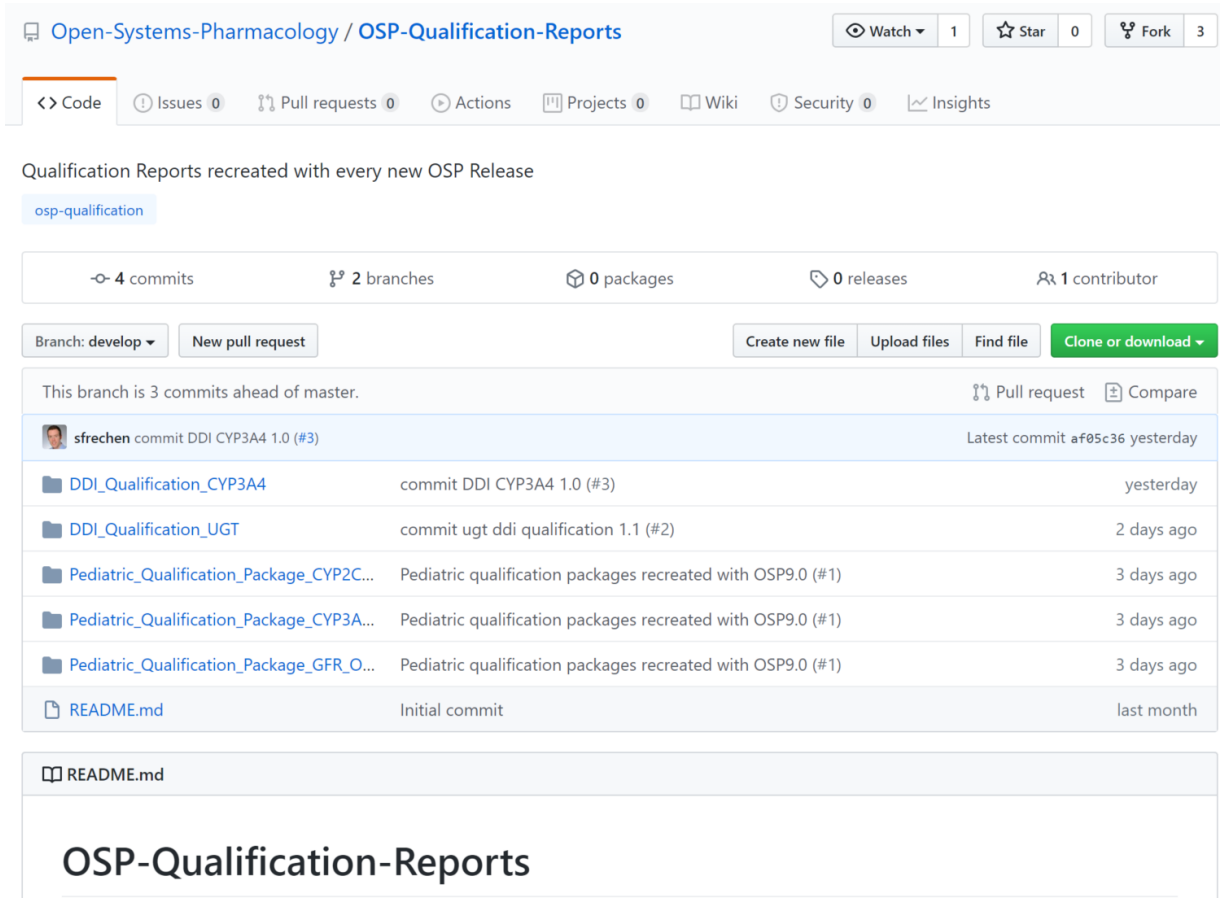
# Community-Driven CoU Qualification Framework
## Qualification Plans Structure

- **PK-Sim snapshots**
- **Observed data** sets (needed for model development and verification)
- Qualification **scenario description** text modules
- Detailed report **settings** to describe the generation of **charts** and qualification **measures**



# Community-Driven CoU Qualification Framework
## OSPS Qualified Model Repository



# Installation Verification

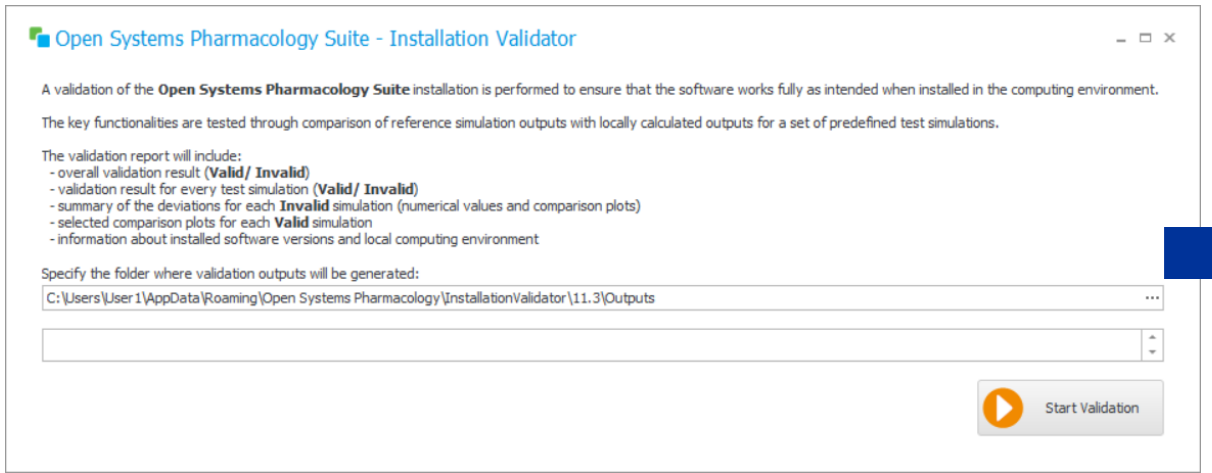
- Installation validation on a target system is ensured by the **fully automated** Installation Validator tool installed as part of the OSP Suite.

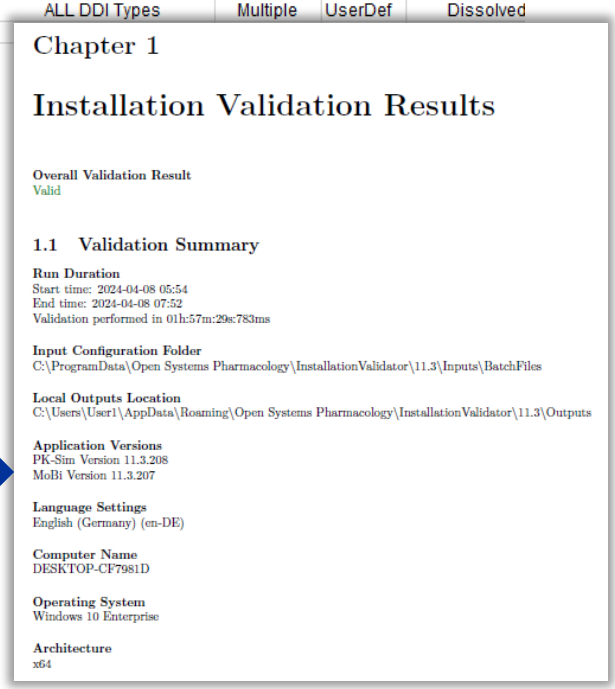
➢ A set of predefined (PBPK) models is being created and simulated in a target modeling environment.

| File | Modell | Simulations | | Individual | | | | | | | Compound | | | | | Application | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 155 | Params | Population | Gender | Age | Aging | Enzymes | Transp. | Bind. | Type | pKa | Partition | Permeab. | Process | Dosing | Type | Formulation |
| Beagle_SingleORAL_Dissolved | 4Comp | 3 | fu/MW/Lipo | Beagle | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | Single | Oral | Dissolved |
| DDI_MultipleCombinations | 4Comp | 23 | --- | ICRP_2002 | MALE | 30 | --- | Multiple | Multiple | --- | small | Multiple | Multiple | Multiple | 1st Order/MM Metab.<br>1st Order/MM Transports<br>ALL DDI Types | Single / Multiple | Oral / IV / UserDef | Dissolved |
| Dog_MultiORAL_12_12_Dissolved | 4Comp | 1 | --- | Dog | --- | --- | --- | --- | --- | --- | small | Acid | RR | Standard | | | | |

➢ Simulation results are compared to the *reference simulation results* (reference simulation results are created and validated during the OSP Release validation).

➢ A **validation report** is generated for the target environment.





Chapter 1

Installation Validation Results

**Overall Validation Result**
Valid

1.1 Validation Summary

**Run Duration**
Start time: 2024-04-08 05:54
End time: 2024-04-08 07:52
Validation performed in 01h:57m:29s:783ms

**Input Configuration Folder**
C:\ProgramData\Open Systems Pharmacology\InstallationValidator\11.3\Inputs\BatchFiles

**Local Outputs Location**
C:\Users\User1\AppData\Roaming\Open Systems Pharmacology\InstallationValidator\11.3\Outputs

**Application Versions**
PK-Sim Version 11.3.208
MoBi Version 11.3.207

**Language Settings**
English (Germany) (en-DE)

**Computer Name**
DESKTOP-CF7981D

**Operating System**
Windows 10 Enterprise

**Architecture**
x64

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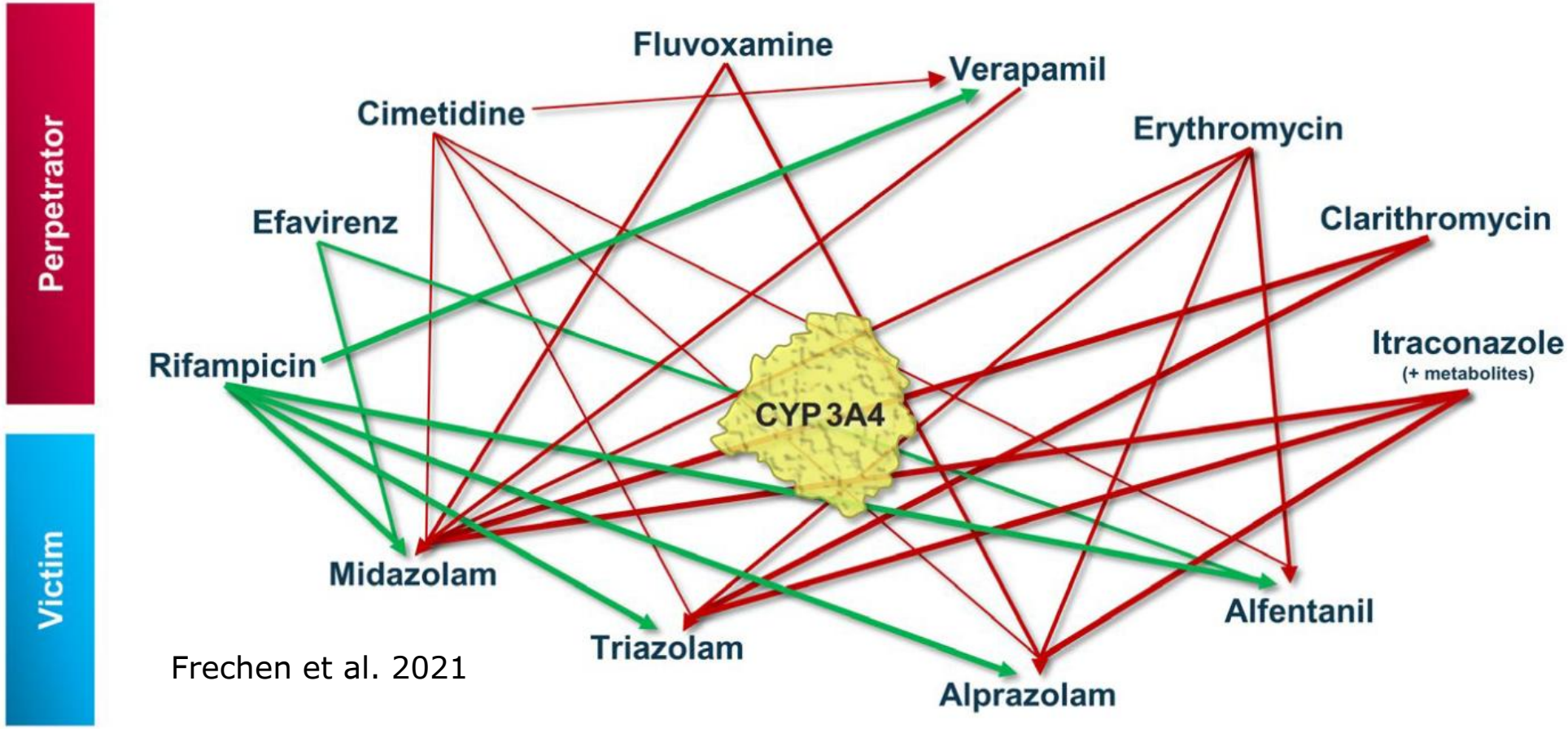
# CoU Qualification in Action: Examples

DDI, pediatrics, special populations - aligned with EMA/FDA frameworks

# Community-Driven CoU Qualification Framework
## Example: CYP3A4 DDI qualification package

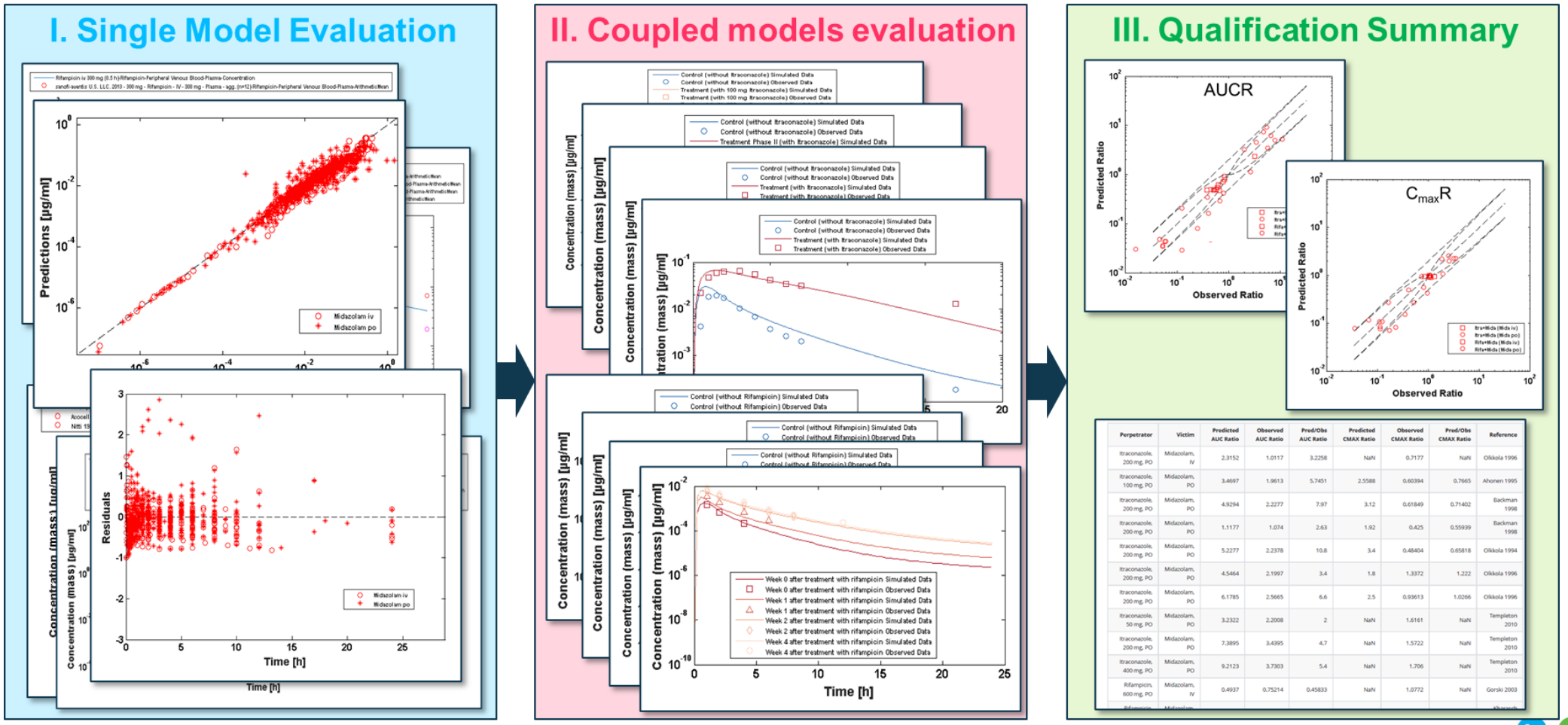
- A complex network of index compounds ranging from strong induction to strong inhibition




Frechen et al. 2021

# Community-Driven CoU Qualification Framework

## Example: CYP3A4 DDI qualification package




| Perpetrator | Victim | Predicted AUC Ratio | Observed AUC Ratio | Pred/Obs AUC Ratio | Predicted CMAX Ratio | Observed CMAX Ratio | Pred/Obs CMAX Ratio | Reference |
|---|---|---|---|---|---|---|---|---|
| Itraconazole, 200 mg, PO | Midazolam, IV | 2.3152 | 1.0117 | 3.2258 | NaN | 0.7177 | NaN | Olkkola 1996 |
| Itraconazole, 100 mg, PO | Midazolam, PO | 3.4697 | 1.9613 | 5.7451 | 2.5588 | 0.60394 | 0.7665 | Ahonen 1995 |
| Itraconazole, 200 mg, PO | Midazolam, PO | 4.9294 | 2.2277 | 7.97 | 3.12 | 0.61849 | 0.71402 | Backman 1998 |
| Itraconazole, 200 mg, PO | Midazolam, PO | 1.1177 | 1.074 | 2.63 | 1.92 | 0.425 | 0.55939 | Backman 1998 |
| Itraconazole, 200 mg, PO | Midazolam, PO | 5.2277 | 2.2378 | 10.8 | 3.4 | 0.48404 | 0.65818 | Olkkola 1994 |
| Itraconazole, 200 mg, PO | Midazolam, PO | 4.5464 | 2.1997 | 3.4 | 1.8 | 1.3372 | 1.222 | Olkkola 1996 |
| Itraconazole, 200 mg, PO | Midazolam, PO | 6.1785 | 2.5665 | 6.6 | 2.5 | 0.93613 | 1.0266 | Olkkola 1996 |
| Itraconazole, 50 mg, PO | Midazolam, PO | 3.2322 | 2.2008 | 2 | NaN | 1.6161 | NaN | Templeton 2010 |
| Itraconazole, 200 mg, PO | Midazolam, PO | 7.3895 | 3.4395 | 4.7 | NaN | 1.5722 | NaN | Templeton 2010 |
| Itraconazole, 400 mg, PO | Midazolam, PO | 9.2123 | 3.7303 | 5.4 | NaN | 1.706 | NaN | Templeton 2010 |
| Rifampicin, 600 mg, PO | Midazolam, IV | 0.4937 | 0.75214 | 0.45833 | NaN | 1.0772 | NaN | Gorski 2003 |



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# Case Study - Successful Regulatory Application

## Finerenone PBPK DDI prediction informs US FDA label

### The finerenone model validated using clinical data with moderate CYP3A inhibitors

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to the FDA's information requests (IRs) submitted on January 28 and March 17, 2021, and concluded the following:

- The finerenone model is adequate to predict the finerenone PK profiles following a single 1 hour intravenous infusion (0.25, 0.5 or 1 mg), a single oral dose administration (1.25, 2.5, 5, 7.5 or 10 mg), or multiple oral dose administration (10 mg BID, 20 mg BID, and 40 mg QD) in healthy subjects.
- The finerenone model is adequate to predict the effect of itraconazole or clarithromycin on finerenone PK following a single oral dose administration of finerenone (10 mg) and multiple dose administration of itraconazole (200 mg BID) or clarithromycin (500 mg BID) in healthy subjects. Model predicted finerenone geometric mean AUC ratio was higher than 5 and 3.5, when co-administered with itraconazole and clarithromycin, respectively, in healthy subjects.
- The finerenone model is adequate to predict the effect of fluvoxamine on finerenone PK following a single oral dose administration of finerenone (10 mg) and multiple dose administration of fluvoxamine (100 mg BID) in healthy subjects. Model predicted finerenone geometric mean AUC ratio was approximately 1.55 when co-administered with fluvoxamine in healthy subjects.
- The finerenone model is adequate to predict the effect of efavirenz on finerenone PK following a single oral dose administration of finerenone (10 mg) and a single dose or multiple dose administration of efavirenz in healthy subjects. Model predicted finerenone geometric mean AUC ratio was approximately 0.2, 0.2, and 0.6, when co-administered with 400 mg QD, 600 mg QD or 400 mg single dose of efavirenz, respectively, in healthy subjects.
- The finerenone model is adequate to predict the effect of rifampicin on finerenone PK following a single oral dose administration of finerenone (10 mg) and multiple dose administration of rifampicin (600 mg QD) in healthy subjects. Model predicted finerenone geometric mean AUC ratio was approximately 0.07 when co-administered with rifampicin in healthy subjects.
- Model extrapolation of clinical study results with moderate inhibitors to the studies with strong modulators may result in uncertainties regarding the predicted exposure change with strong modulators.

Taken from:
FDA - CENTER FOR DRUG EVALUATION AND RESEARCH
Intergated Review
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=215341

**→PBPK Review**
p. 202 - 211

# Addressing EMA Qualification Requirements

- **Direct alignment with EMA qualification requirements:**
  - Platform Qualification and Validation ✓
  - External evidence benchmarking and Model Evaluations ✓
  - Clearly defined processes for development and qualification/validation ✓
  - Version control & lifecycle ✓

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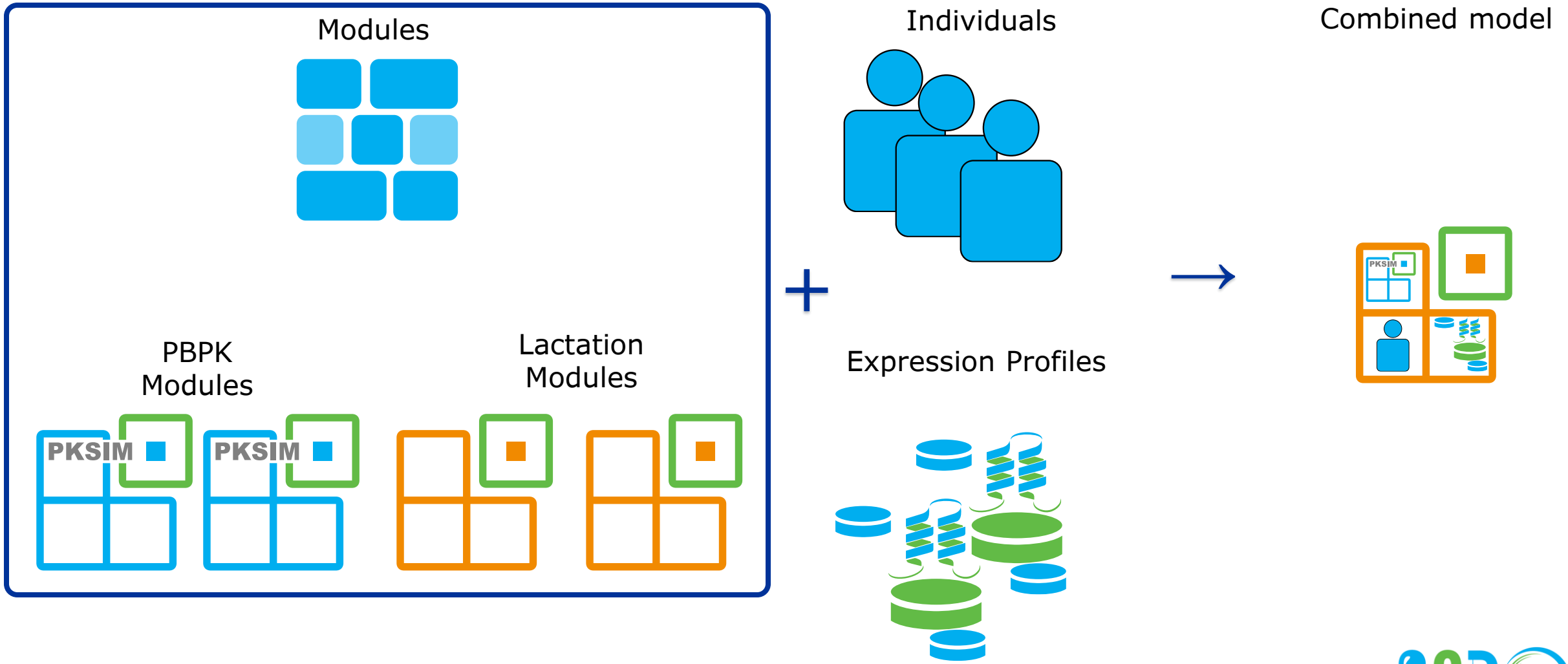
# Beyond PBPK: The Modular MIDD Future

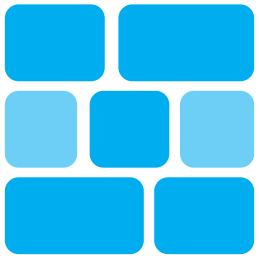
## Expanding to PBPK-QSP integration and qualification for complex translational models

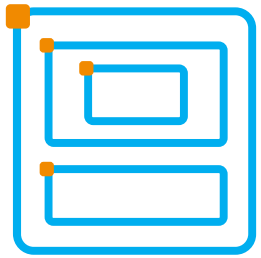
# Modular M&S Concept of OSP V12+
## Model Building Approach



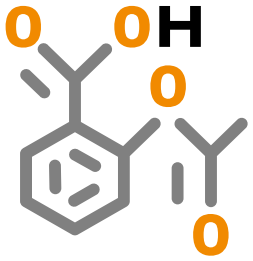
# Modular M&S Concept of OSP V12+
## Model Building Approach

A module

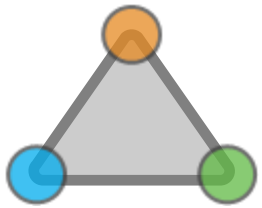




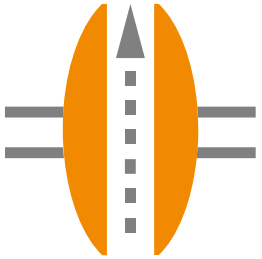
Spatial Structure




Molecules



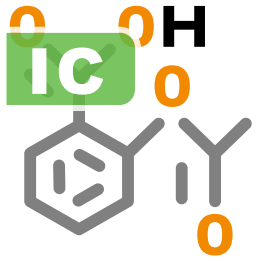
Reactions



Passive Transports

Observers

Events

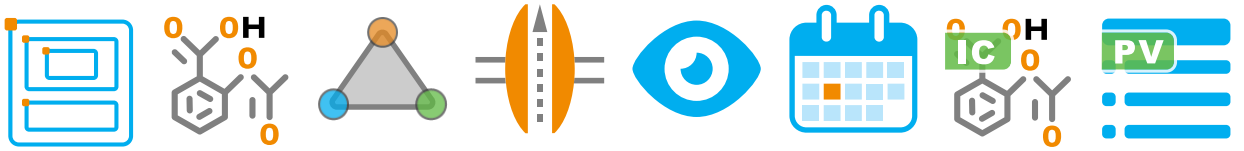



Initial Conditions

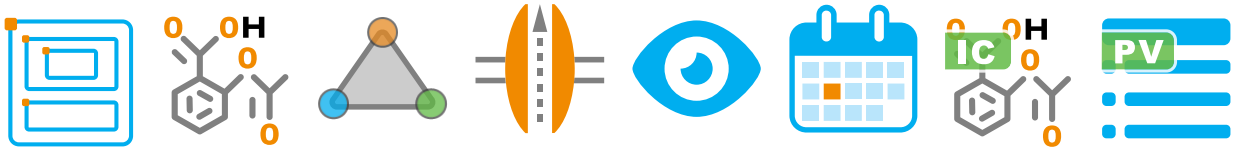

Parameter Values

# Modular M&S Concept of OSP V12+
## Model Building Approach

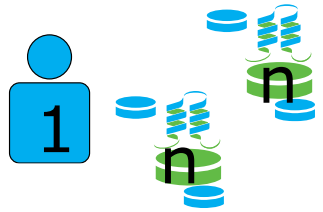
CompoundA




CompoundB

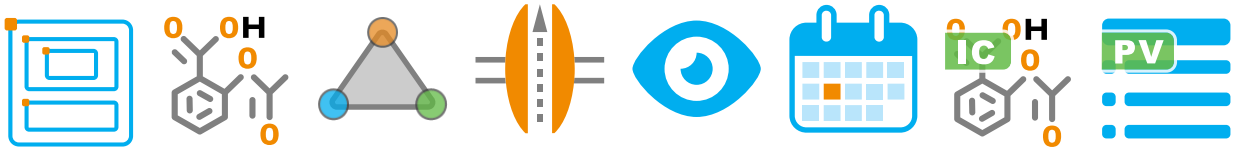



31 years old female extensive metabolizer

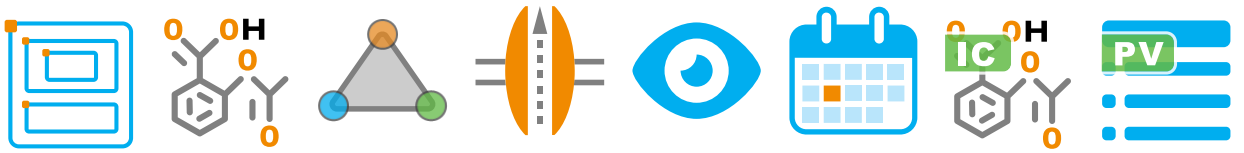


# Modular M&S Concept of OSP V12+
## Model Building Approach

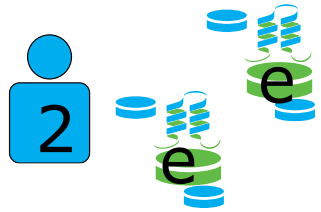
CompoundA




CompoundB

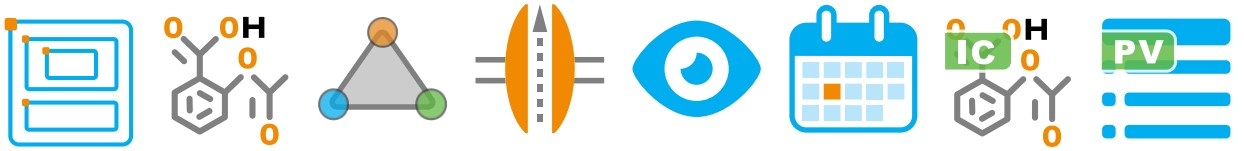



31 years old female extensive metabolizer



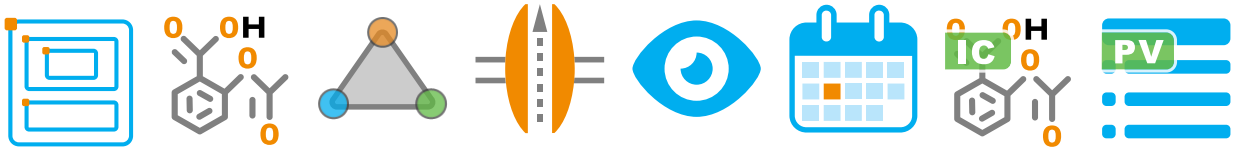
# Modular M&S Concept of OSP V12+
## Model Building Approach


CompoundA

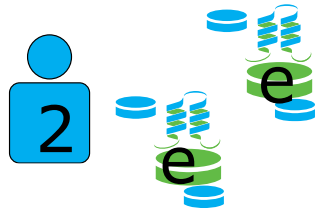


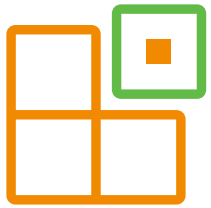


CompoundB

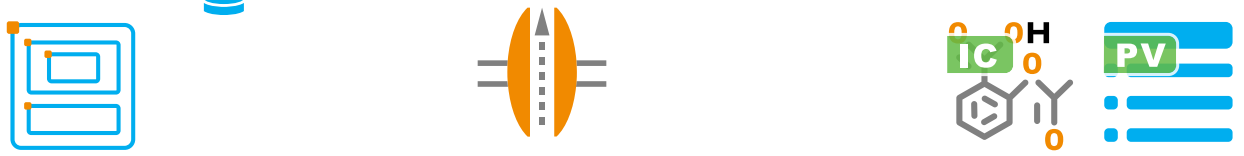



31 years old female extensive metabolizer



Pregnancy

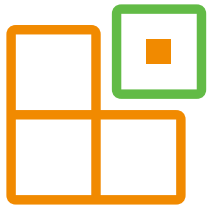


# Modular M&S Concept of OSP V12+
## Model Building Approach

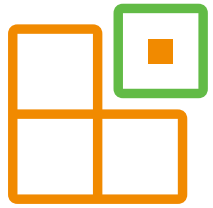

CompoundA


CompoundB

31 years old female extensive metabolizer



Pregnancy



CompoundA effect model
Healthy population

# Modular M&S Concept of OSP V12+
## Model Building Approach

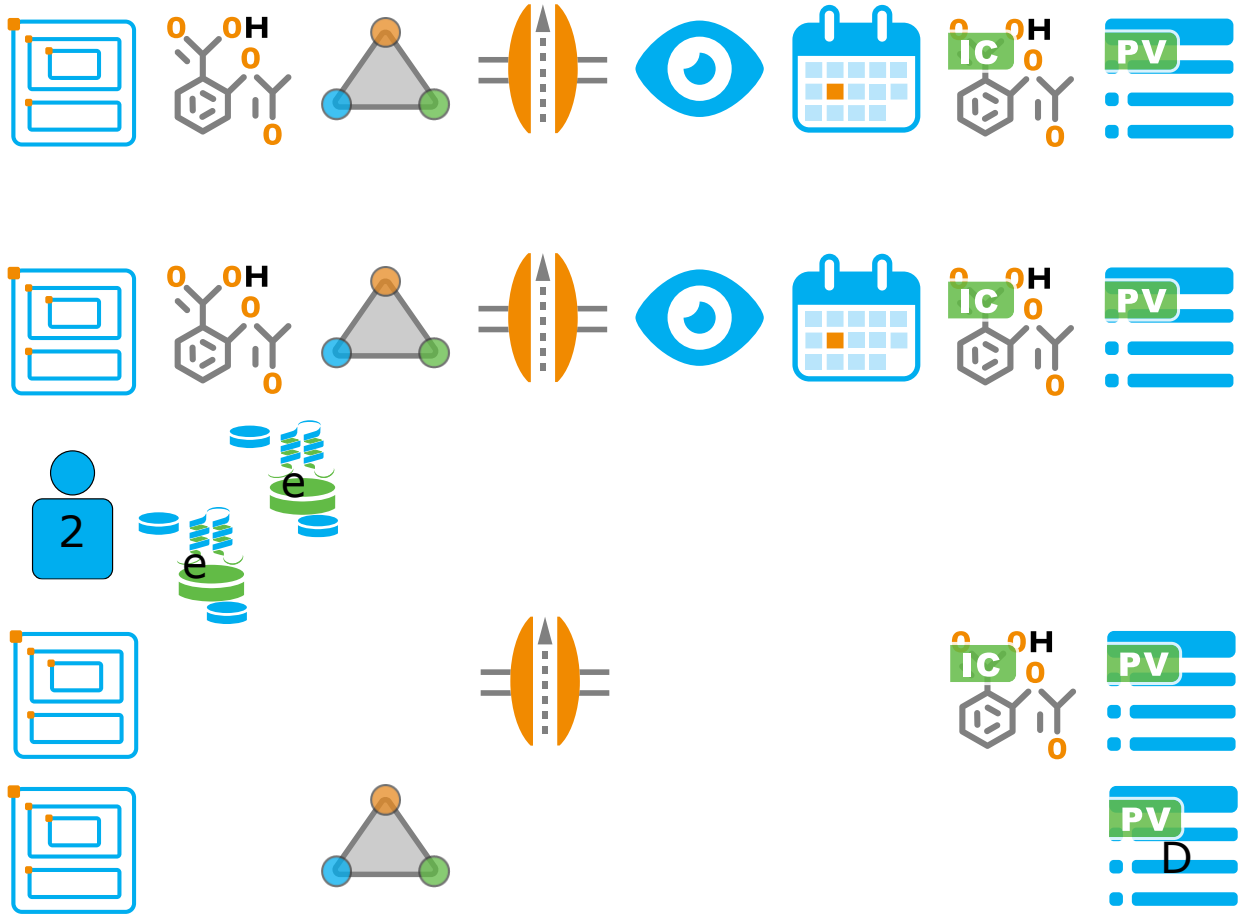

CompoundA


CompoundB

31 years old female extensive metabolizer

Pregnancy

CompoundA effect model
Disease population



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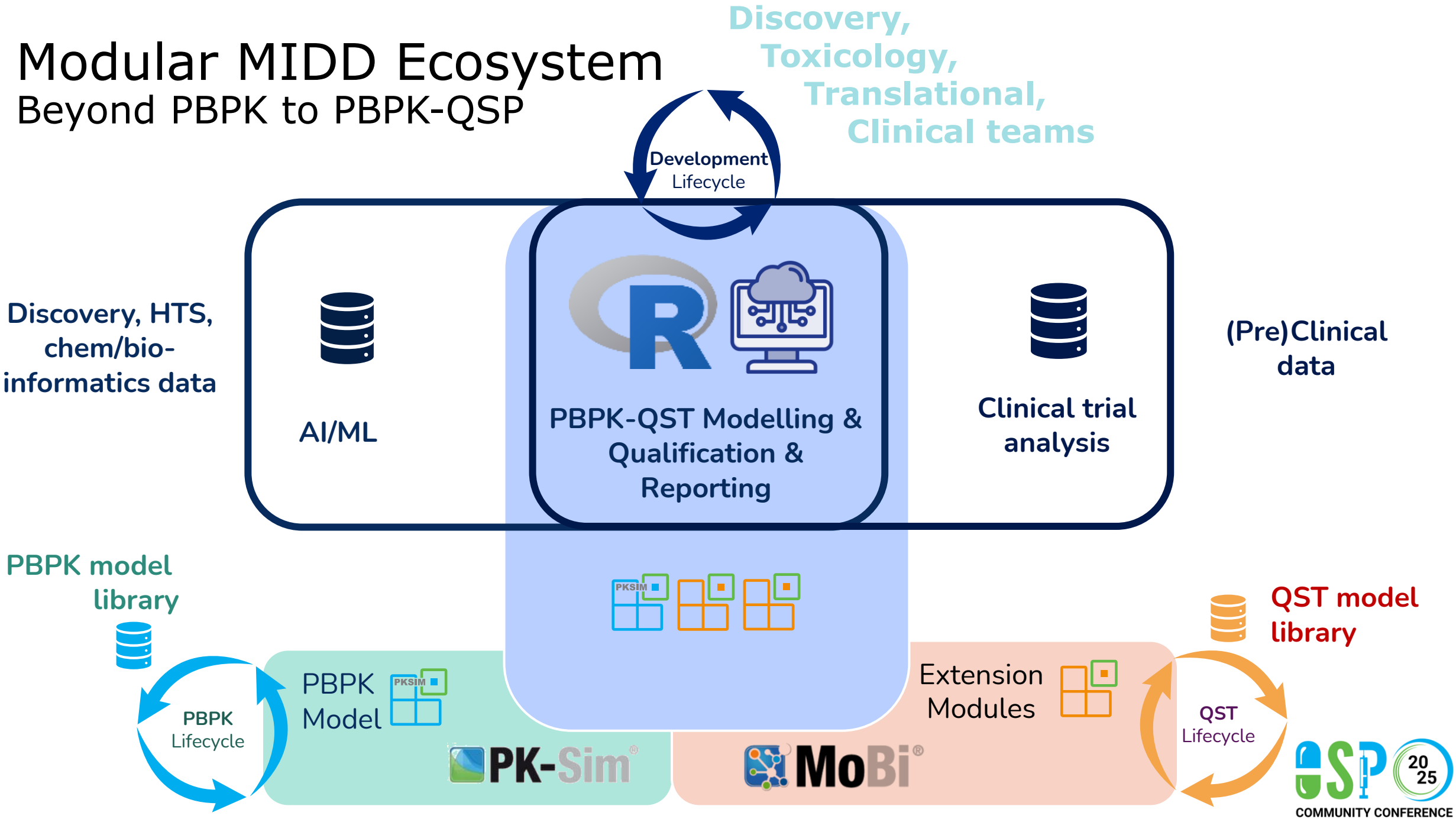
# Modular MIDD Ecosystem

## Beyond PBPK to PBPK-QSP



# Modular MIDD Ecosystem
## Supportive (R-based) Packages / Workflows

1

PK-Sim®

MoBi®

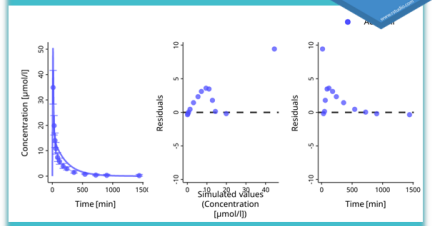
Model development

2

1. Species
2. Models/Modules
3. Individual/pop
4. Parameterization
5. Dosing Scheme

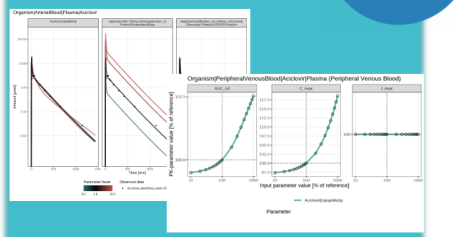
Scenarios definition

3



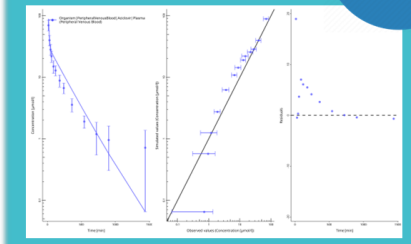

Plot definition

4



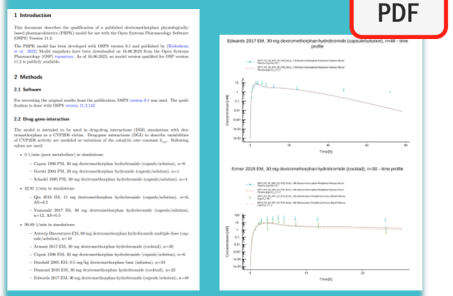
Sensitivity analysis

5



Parameter identification

6




Report generation



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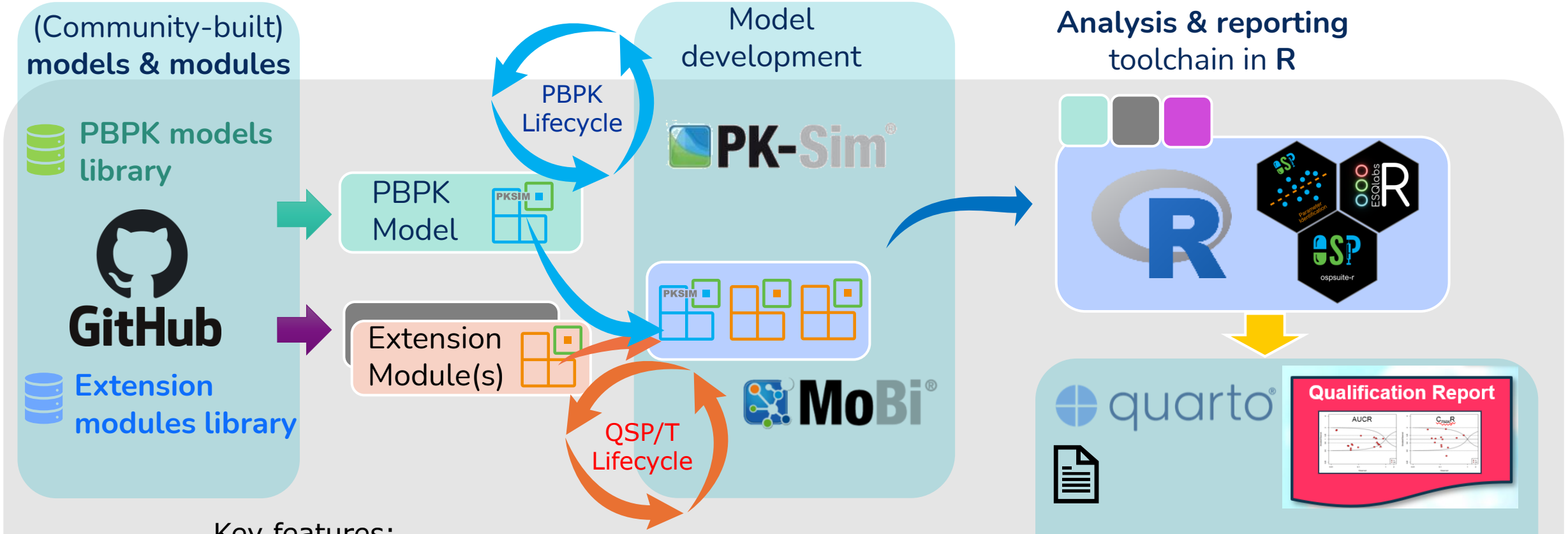
# Modular MIDD Ecosystem

## Qualification and Reporting with the Modularization Concept




Key features:

- Decoupled qualification (PBPK + QSP with MoBi-R)
- Component reusability
- Collaborative model development


# Take-Aways

OSP = Equitable high-quality Solutions for Mechanistic Model Development and Qualification

# Community Impact & Adoption

- OSP Community Conference (~100 Participants yearly)
- Online Training Platform (ESQlabs, ~200 subscribers)
- Workshops by CROS (ESQlabs, Pharmetheus, BioNotus, …)
- ~ 100 Peer Reviewed Publications in 2024
- Regulatory Submissions:


| Drug name | Company | Indication | Link | Software |
|---|---|---|---|---|
| Vesicare LS (Solifenacin) | Astellas | Neurogenic detrusor overactivity (NDO) | https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/209529Orig1s000ClinPharmR.pdf | PK-Sim® v5.1 |
| Kerendia (Finerenone) | Bayer | Chronic kidney disease (CKD) | https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215341Orig1s000IntegratedR.pdf | PK-Sim V7.4 and 9.1 |
| Verquvo (Vericiguat) | MSD | Heart failure (HF) | https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214377Orig1s000IntegratedR.pdf | PK-Sim V7.1 and MoBi V7.1 |



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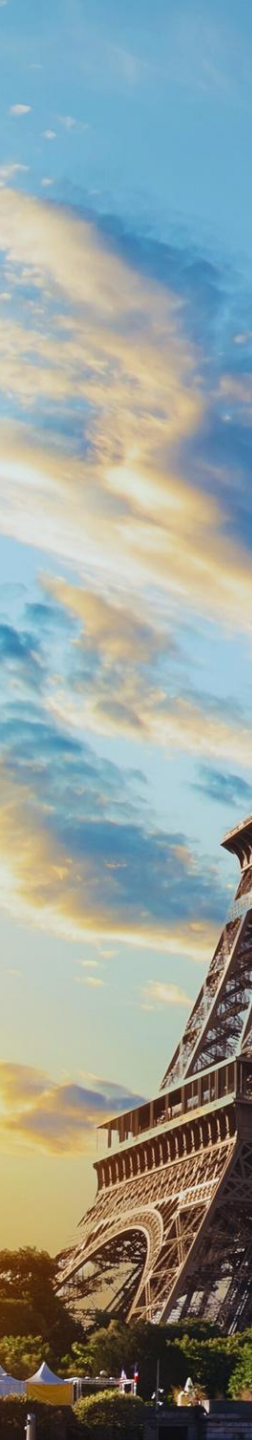
# Future Vision & Call to Action

- **Streamlining regulatory qualification:**
  - Standardized (Cross-platform / Cross-agency) qualification templates
  - Cross-platform benchmarking
  - Regulatory agency collaboration
  - Data sharing across stakeholders

- OSP Initiates preparations for submissions to FDA MMF and EMA Qualification

# Conclusions

- **Key takeaways:**
  - Open source ≠ lower quality, and = higher quality with a community
  - Transparency builds trust
  - Community approach enables transparent qualification
  - Framework ready for regulatory use



# Wider Acknowledgements

- OSP Management Team members
- Funding agencies (EU, BMBF, Gates, EFSA, NC3R, …)
- Community contributors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Thank you
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