



# The Qualification Concept of OSP and its exemplary application to DDI and pediatric predictions with PK-Sim

Session 3, PK-Sim/MoBi FDA Workshop  
20<sup>th</sup> April 2021

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# Session 3 Agenda

1. Open Systems Pharmacology (OSP) Introduction
  2. A Generic Framework for the PBPK Platform Qualification of PK-Sim
  3. Platform Qualification Showcase: Predicting CYP3A4-mediated DDI
- Break**
4. Pediatric PBPK Application
  5. *Hands-On:* Derive optimal doses for children

# *Open Systems Pharmacology*

## Vision

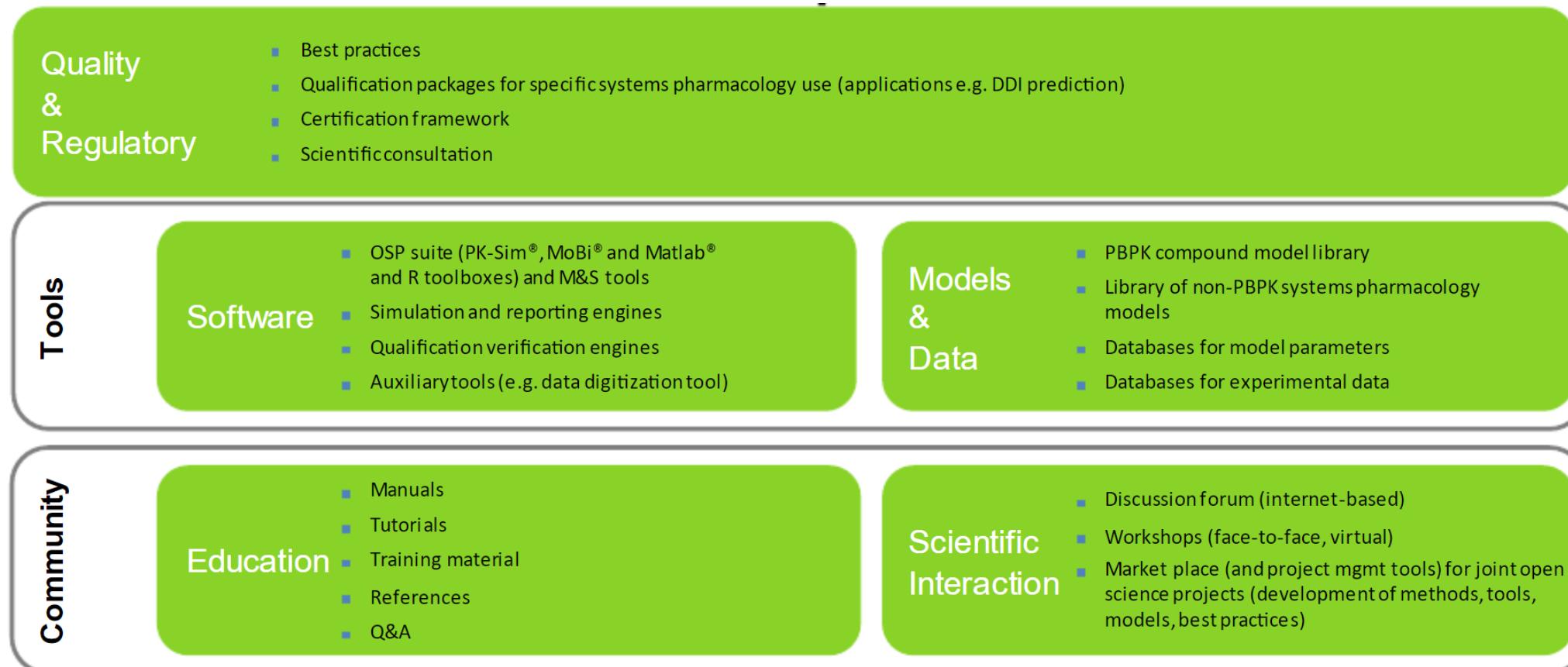
Robust and reliable, easy-to-use modeling & simulation tools, processes and models for pharmaceutical and other life-sciences applications. Qualified and accepted by a scientific community from academia, regulatory agencies and industry. Available and open to everyone.



## 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 scope of OSP addresses high priority applications of Systems Pharmacology and the need to continuously develop the scientific, methodological and regulatory foundation together with the software platform



OSP Management Team coordinates the interplay of focus areas and interfaces between them. Dedicated Focus Groups conceptualize, design and progress the individual areas.

OSP Management Team organize coordination and oversee all activities (bi-weekly meetings)

- Rolf Burghaus, Bayer AG
- Andrea Edginton, University of Waterloo
- Valvanera Vozmediano Esteban, University of Florida
- Andreas Kovar, Sanofi
- Thorsten Lehr, Universität des Saarlandes
- Jörg Lippert, Bayer AG
- Dr. José David Gómez Mantilla, Boehringer Ingelheim
- Matthew M. Riggs, Metrum Research Group
- Stephan Schaller (Chair), esqLABS
- Michael Sevestre, Design2Code
- Erik Sjögren, Pharmetheus, Uppsala University
- Juri Solodenko, Bayer AG
- Alexander Staab, Boehringer Ingelheim
- Donato Teutonico, Sanofi

OSP Sounding Board provides scientific/technical consultancy to MT and informs on trends (yearly meeting with MT)

- Sebastian Frechen, Bayer AG
- Mats Karlsson, Uppsala University
- Peter Milligan, Pharmetheus
- Jan Schlender, Bayer AG

Focus groups are expected to conceptualize and coordinate activities of the respective field.  
Includes a OSP MT sponsor, a chair and OSP community members.

# Current Focus Groups (1/2)

Focus Group	Objective	Lead (GitHub UserID)
<b>Absorption</b>	<p>The addition of model structures defining additional routes of administration/absorption is required to expand the application scope of the software in a consistent manner across users. The overall objectives are to define processes for</p> <ol style="list-style-type: none"> <li>1. Technical generation of new routes of absorption destined for the OSP Suite</li> <li>2. Evaluation of those absorption modules.</li> </ol>	Erik Sjörgren (Erik-Sjogren)
<b>Automation</b>	Automation is a strategic theme of the OSP MT. Automation obviously is a means to increase efficacy but also enables the execution of large technical tasks like population or trials simulations that cannot be conducted manually. Due to its intrinsic transparency, automation is an element of quality by design.	Juri Solodenko (Yuri05)
<b>Community engagement</b>	<ul style="list-style-type: none"> <li>• To streamline official outside communication channels of OSP <ul style="list-style-type: none"> <li>- Social Media: LinkedIn / Twitter</li> <li>- Newsletter / OSP News Section</li> <li>- OSP Booth at conferences</li> <li>- OSP Events (Hackathon, ...)</li> </ul> </li> <li>• Use Communication Channels to increase community engagement</li> <li>• Obtain statements of endorsement</li> <li>• Sustain Community Collaboration Framework</li> </ul>	Stephan Schaller (StephanSchaller)
<b>DDI</b>	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)
<b>IVIVE</b>	<ul style="list-style-type: none"> <li>• Improve and facilitate use of IVIVE in PK-Sim</li> <li>• Provide guidelines on how to conduct IVIVE in PK-Sim</li> <li>• Facilitate integration of in vitro data in prediction of DDI (e.g. integration of fraction metabolized)</li> <li>• Extrapolation of Caco-2 permeabilities to effective permeabilities</li> </ul>	Donato Teutonico (teutonicod)

# Current Focus Groups (2/2)

Focus Group	Objective	Lead (GitHub UserID)
<b>PBPK best practices</b>	<p>Establishing Standards for PBPK Model Development and Application to Ensure Reliability, Reproducibility and Transparency, Independent of Modeling Platform.</p> <p>The standards should be considered when developing a PBPK model, regardless of the platform.</p> <p>Not a how-to-guide</p>	Matthew Riggs (riggsmm)
<b>PD</b>	<ul style="list-style-type: none"> <li>PBPK/PD &amp; QSP modeling is a strategic theme of the OSP MT</li> <li>Identify needs for enabling / facilitating PD/QSP modelling in PK-Sim and MoBi</li> <li>To streamline PD efforts of OSP</li> <li>Derive a strategy for / identify public or industrial collaborations or funding sources to sponsor roadmap implementation</li> </ul>	Stephan Schaller (StephanSchaller)
<b>Special populations</b>	<p>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</p> <ol style="list-style-type: none"> <li>technical generation of populations destined for the OSP Suite and,</li> <li>evaluation of those populations.</li> </ol> <p>This protocol will allow populations to be added more efficiently.</p>	Andrea Edginton (Aedginto)
<b>Statistical Modelling</b>	<p>Statistical Modeling is a strategic theme of the OSP MT. Statistical modeling is a key enabler for PBPK and QSP M&amp;S. Respective capabilities are required for all application areas to quantitatively assess population variability and uncertainty in prior knowledge and posterior results.</p>	Christian Diedrich (DiedrichC)
<b>Suite Release Mgmt. / Software Usability</b>	<p>The software suite is a pillar and the nucleus of OSP. Development and maintenance of the suite is a core element of the OSP mission. Active Release Management is required to execute on this mission.</p>	Juri Solodenko (Yuri05)

# Managed Open Source

- OSP Suite uses **GitHub** (<https://github.com>) as a source control platform
- Release planning is realized via the GitHub “Projects” feature. Issues are organized by milestones and effort estimates are proposed and tracked. All of these efforts can be seen by anyone. Release planning and release are only done by the core development team that is supported by Bayer.
- Approved “official” releases of the OSP Suite are published on the GitHub Platform and can be downloaded by any user (no GitHub account is required for this). Full release histories are available.
- Rigorous software development practices uses Continuous Integration (CI) that includes test automation, build automation, code quality analysis and artifact repository. Nightly builds are accessible to anyone and thus always in beta mode for the future version.

# OSP Sessions

1. Introduction to PK-Sim
2. PK-Sim applied for modeling of oral drug absorption
3. The Qualification Concept of OSP and its exemplary application to DDI and pediatric predictions with PK-Sim
4. Application of PBPK modeling of locally acting drugs – possibilities and considerations



A Generic Framework for the PBPK  
Platform Qualification of PK-Sim

# PBPK impact vs. requirements

- PBPK is increasingly used in numerous application areas
  - to guide decision-making during drug development and
  - evaluate clinically untested scenarios for the support of prescription drug labeling.
- Regulatory agencies now even recommend the use of PBPK under certain conditions to evaluate the DDI risk for new investigational drugs both as victim or as perpetrator.
- Regulatory agencies now increasingly demand that sponsors of PBPK studies need to explicitly demonstrate the predictive capability of the PBPK platform for a particular context of use.
  - EMA: version-specific PBPK platform **qualification** for the intended purposes
  - FDA: demonstration of the **level of confidence** in PBPK analyses for their intended uses

# Motivation for a generic qualification framework

While several reports demonstrated a good predictive performance for different PBPK platforms in various application areas, all these potential ‘qualifications’ reflect just a **snapshot in time** in terms of a temporary qualification of the current version of the respective PBPK platform.

Prediction of drug-drug interactions in pharmacokinetic and pharmacodynamic modeling of drugs Simcyp Predictive Performance of Physiologically Based Pharmacokinetic and Population

PBPK Models for CYP3A4 and P-gp DDI Prediction A Modeling Network of Rifampicin, Itraconazole, Clarithromycin, Midazolam, Alfentanil, and Digoxin

Nina Hanke<sup>1</sup>, Sebastian Frechen<sup>2</sup>, Daniel Moj<sup>1</sup>, Hannah Britz<sup>1</sup>, Thomas Eissing<sup>2</sup>, Thomas Wendl<sup>2</sup> and Thomas

Predictive Performance of Physiologically Based Pharmacokinetic (PBPK) Modeling of Drugs

**Predictive Performance of Physiologically Based Pharmacokinetic and Population**

A Physiologically-Based Pharmacokinetic (PBPK) Model Network for the Prediction of CYP1A2 and CYP2C19 Drug–Drug–Gene Interactions with Fluvoxamine, Omeprazole, S-mephenytoin, Moclobemide, Tizanidine, Mexiletine, Ethinylestradiol, and Caffeine

Tobias Kanacher <sup>1,†</sup>, Andreas Lindauer <sup>1,‡</sup>, Enrica Mezzalana <sup>1,†</sup>, Ingrid Michon <sup>1,§</sup>, Celine Veau <sup>2</sup>, Jose David Gómez Mantilla <sup>2</sup>, Valerie Nock <sup>2</sup> and Angèle Fleury <sup>2,\*</sup>

# Properties of the technical framework

- generate comprehensive **standardized reports** to facilitate efficient review
- enable efficient **re-qualification** (e.g. for upcoming new PK-Sim® versions) via an **automated workflow**
- enable **agile** and **versatile** development of qualification scenarios (extensions, tailoring, etc.)
- provide full **transparency** and **traceability**
- allow **collaborative development** of (publicly available) qualification scenarios

# Automatic (Re-)Qualification Framework

**Core:** an automated workflow that generates comprehensive *qualification reports* based on prespecified dedicated *qualification plans*.

## Qualification report

- a document structured in chapters, beginning with a short description of the scientific background of the qualification scenario, followed by a brief methodological description (e.g. modeling strategy, available data) and the presentation of the results

## Qualification plan

- a technical document (in JSON format) that contains all information to generate such a qualification report
- defines how *static* text-module content and *dynamic* simulation-based content will be combined
  - static text modules will be taken as is and inserted into the report
  - dynamic content is newly produced with every execution of the qualification workflow and may change between OSP versions in case of differences between the previous and new model structures/parameterizations

# Qualification Plan

- developed, maintained and released within a dedicated qualification repository with a proper release management  
(e.g. <https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4>)
- consists of the following main sections
  - **Projects:** defines references to all project repositories of PBPK substance *model snapshots* (file in JSON format) and potential dependencies with inheritance of certain building blocks between projects. A model snapshot contains only the minimal amount of information required to set-up the compound's PBPK model file including simulations from scratch in (a new version of) PK-Sim®; this includes in particular primary substance-specific input parameters (e.g. molecular weight, lipophilicity, etc.)
  - **ObservedDataSets:** reference to required observed pharmacokinetic (PK) data
  - **Sections:** defines the chapter structure of the report and links to respective static text modules
  - **Plots:** defines desired figures, tables and qualification measures. Various predefined plot types are available, such as concentration-time profile plots, goodness of fit plots, etc.

# Qualification Plan

```
{  
  "$schema": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/QualificationPlan/v2.2/schemas/OSP_Qualification_Plan_Schema.json",  
  "Projects": [...  
  ],  
  "ObservedDataSets": [...  
  ],  
  "Plots": {  
    "AxesSettings": {...  
    },  
    "PlotSettings": {...  
    },  
    "AllPlots": [],  
    "GOFMergedPlots": [],  
    "ComparisonTimeProfilePlots": [...  
    ],  
    "DDIRatioPlots": [...  
    ]  
  },  
  "Inputs": [],  
  "Sections": [...  
  ],  
  "Intro": [...  
  ]  
}
```

# Qualification Plan

```
{
  "$schema": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/OsP-Qualification-Plan/v2.2/schemas/OSP_Qualification_Plan_Schema.json",
  "Projects": [
    {
      "Id": "Alfentanil",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Alfentanil-Model/v2.1/Alfentanil-Model.json"
    },
    {
      "Id": "Alprazolam",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Alprazolam-Model/v1.0/Alprazolam-Model.json"
    },
    {
      "Id": "Cimetidine",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Cimetidine-Model/v1.0/Cimetidine-Model.json"
    },
    {
      "Id": "Clarithromycin",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Clarithromycin-Model/v1.1/Clarithromycin-Model.json"
    },
    {
      "Id": "Efavirenz",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Efavirenz-Model/v1.0/Efavirenz-Model.json"
    },
    {
      "Id": "Erythromycin",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Erythromycin-Model/v1.1/Erythromycin-Model.json"
    },
    {
      "Id": "Fluvoxamine",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Fluvoxamine-Model/v1.1/Fluvoxamine-Model.json"
    },
    {
      "Id": "Itraconazole",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Itraconazole-Model/v1.2/Itraconazole-Model.json"
    },
    {
      "Id": "Midazolam",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Midazolam-Model/v1.0/Midazolam-Model.json"
    },
    {
      "Id": "Rifampicin",
      "Path": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Rifampicin-Model/v1.1/Rifampicin-Model.json"
    }
  ],
  "Inputs": [],
  "Sections": [...],
  "Intro": [...]
}
```

# Qualification Plan

```
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  "$schema": "https://raw.githubusercontent.com/OSPharmacology/OSP-Qualification/master/qualification_plan_schema.json",
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  "ObservedDataSets": [...],
  "Plots": {
    "AxesSettings": {...},
    "PlotSettings": {...},
    "AllPlots": [],
    "GOFMergedPlots": [],
    "ComparisonTimeProfilePlots": [...],
    "DDIRatioPlots": [
      {
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        "Title": "CYP3A4 DDI",
        "PKParameter": "AUC|CMAX",
        "PlotType": "predictedVsObserved|residualsVsObserved",
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          "GMFE",
          "Measure",
          "Table"
        ],
        "Groups": [
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            "Caption": "Cimetidine + Alfentanil (iv)",
            "Color": "#FF0000",
            "Symbol": "Square",
            "DDIRatios": [
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                "Output": "Organism|PeripheralVenousBlood|Alfentanil|Plasma (Peripheral Venous Blood)",
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                  "Project": "Cimetidine-Alfentanil-DDI",
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                  "EndTime": "Inf",
                  "TimeUnit": "h"
                }
              }
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      }
    ],
    "Inputs": [],
    "Sections": [...],
    "Intro": [...]
  }
}
```

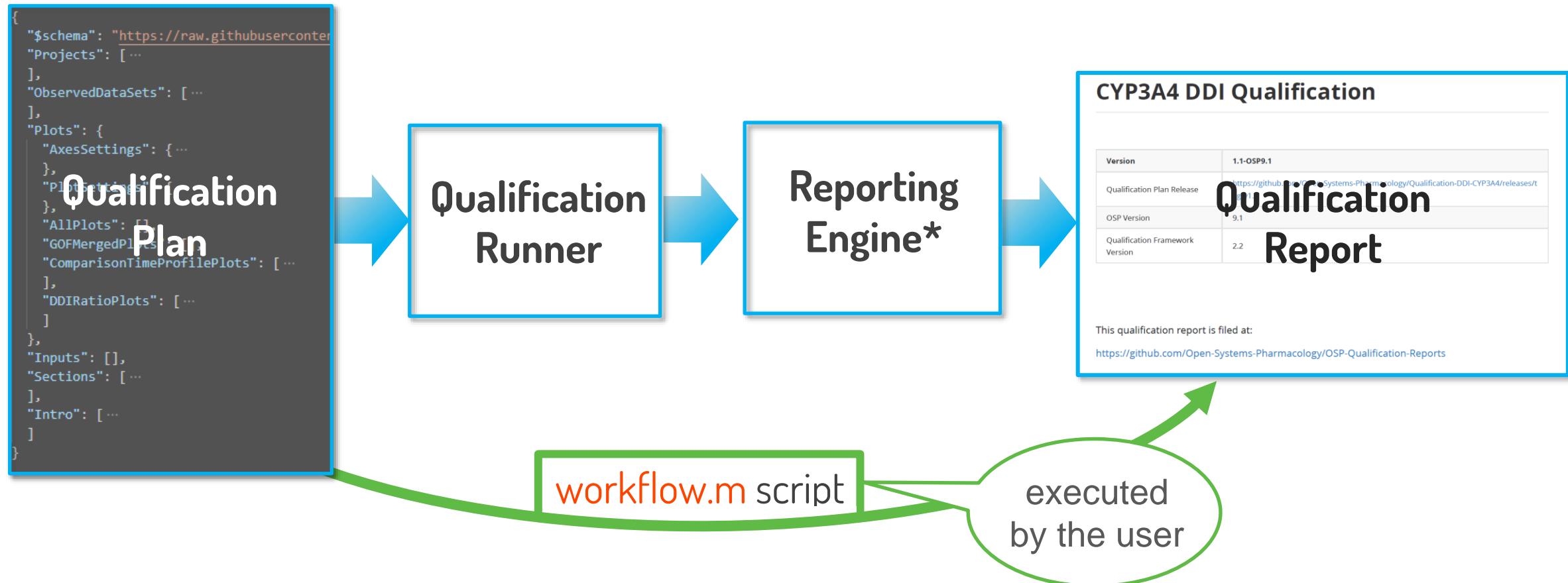
# Qualification Plan

```
{
  "$schema": "https://raw.githubusercontent.com/Open-Sys-Pharm/Qualification-JSON-Schema/main/QualificationPlan.schema.json",
  "Projects": [...],
  "ObservedDataSets": [...],
  "Plots": {
    "AxesSettings": {...},
    "PlotSettings": {...},
    "AllPlots": [],
    "GOFMergedPlots": [],
    "ComparisonTimeProfilePlot": [...],
    "DDIRatioPlots": [...]
  },
  "Inputs": [],
  "Sections": [...],
  "Intro": [...]
}

{
  "Sections": [
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      "Title": "1 Introduction",
      "Content": "https://raw.githubusercontent.com/Open-Systems-Pharmacology/Qualification-text-modules/v1.0/Empty.md",
      "Sections": []
    },
    {
      "Id": 11,
      "Title": "1.1 Objective",
      "Content": "Content/Qualification_DDI_CYP3A4_objective.md"
    },
    {
      "Id": 12,
      "Title": "1.2 CYP3A4 DDI Network",
      "Content": "Content/Qualification_DDI_CYP3A4_network_description.md",
      "Sections": [
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          "Title": "Cimetidine - Alfentanil DDI",
          "Content": "Content/Cimetidine-Midazolam-DDI.md"
        },
        {
          "Id": 1202,
          "Title": "Cimetidine - Alprazolam DDI",
          "Content": "Content/Cimetidine-Midazolam-DDI.md"
        },
        {
          "Id": 1203,
          "Title": "Cimetidine - Midazolam DDI",
          "Content": "Content/Cimetidine-Midazolam-DDI.md"
        },
        {
          "Id": 1204,
          "Title": "Cimetidine - Triazolam DDI",
          "Content": "Content/Cimetidine-Midazolam-DDI.md"
        }
      ]
    }
  ]
}
```

# From Plan to Report...

...dedicated software tools were developed.



Software available at: <https://github.com/Open-Systems-Pharmacology/QualificationPlan/releases>

\* Reporting Engine currently released as **Matlab Code**, transfer to **R** in development.

# From Plan to Report...

...dedicated software tools were developed.

```

% Script to perform a Qualification Plan workflow
% Qualification Plan Workflow developed with Matlab 2017b
%
% -----
%
close all
clear all
tic

%
% -----%
% replace qualificationRunnerFolder and markdownJoinerFolder with your paths
qualificationRunnerFolder = 'C:\Software\QualificationRunner9.1.1';
markdownJoinerFolder = 'C:\Software\markdown-joiner';
PKSimPortableFolder = 'C:\Software\PKSim9.1.2';

%
% -----%
% replace baseDir and qualificationPlanName with your paths
%
% assuming the following structure
%   - baseDir
%     - input
%       - qualificationPlanName
%     - re_input
%     - re_output
%     - report
%
baseDir = fullfile(cd);
qualificationPlanName = 'qualification_plan.json';

% In case your folder structure is different from assumed above,
% qualificationPlan, REInput_path, REOutput_path and ReportOutput_path must be adjusted as well
%
% - REInput_path: input path for the Reporting engine
%   (corresponds to the output path defined in the Qualification Runner)
%
% - REOutput_path: outputs of the Reporting Engine will be created here
%   CAUTION: if the folder is not empty, its contents will be deleted
%
% - ReportOutput_path: final report will be generated here
qualificationPlan = fullfile(baseDir,'input',qualificationPlanName);
REInput_path = fullfile(baseDir,'re_input_n2');
REOutput_path = fullfile(baseDir,'re_output_n2');
ReportOutput_path=fullfile(baseDir,'report_n2');

%
% -----%
% STEP #1: start qualification runner to generate inputs for the reporting engine
startQualificationRunner(qualificationRunnerFolder, qualificationPlan, REInput_path, ['-p ' PKSimPortableFolder]);
%
```

```

% -----
% STEP #2: start reporting engine
% Get the Configuration Plan Settings
reportConfigurationPlan = 'report-configuration-plan.json';
[WSettings, ConfigurationPlan, TaskList, ObservedDataSets] = initializeQualificationWorkflow(reportConfigurationPlan, REInput_path, REOutput_path);

%OPTIONAL: set watermark. If set, it will appear in all generated plots
WSettings.Watermark = '';

% run the Workflow tasklist of ConfigurationPlan
SubunitsForDDIPlot = {'Mechanism','Perpetrator','Victim'}; % e.g. {'Mechanism', 'Perpetrator', 'Victim'}
runQualificationWorkflow(WSettings, ConfigurationPlan, TaskList, ObservedDataSets, SubunitsForDDIPlot);

QualificationWorkflowTime = toc/60;
fprintf('\n Qualification Workflow Duration: %0.1f minutes \n', QualificationWorkflowTime);

%
% -----%
% STEP #3: call MarkdownJoiner to combine Reporting Engine output into the final report
MarkdownJoiner_path=fullfile(markdownJoinerFolder,'markdown-joiner.exe');

% alternative #1: ReportOutput_path must be empty. If not, report generation will fail
status = system(['''' MarkdownJoiner_path "' -i "' REOutput_path "' -o "' ReportOutput_path '''']);

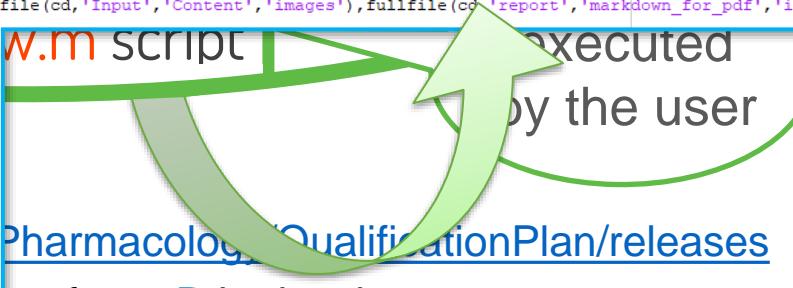
% alternative #2: (CAUTION) ReportOutput_path will be cleared first
%status = system(['''' MarkdownJoiner_path "' -i "' REOutput_path "' -o "' ReportOutput_path "' -f'''']);

if status~=0 error('MarkdownJoiner failed'); end

% Copy additional files

copyfile(fullfile(cd,'Input','Content','images'),fullfile(cd,'report','markdown_for_github','images'));
copyfile(fullfile(cd,'Input','Content','images'),fullfile(cd,'report','markdown_for_pdf','images'));

```

**W.M SCRIPT**  **executed by the user**

[Pharmacology/QualificationPlan/releases](https://github.com/Pharmacology/QualificationPlan/releases)  **transfer to R in development.**

# Model evaluation reports

- The workflow cannot only be used to generate qualification reports for entire qualification scenarios but also to generate *model evaluation reports* for single PBPK substance models
- These documents provide a report on the particular modeling strategy, model development, input parameters, model features and model performance (regarding the description of the respective compound's PK)
- Similar to a qualification plan, an *evaluation plan* comprises all information needed to generate the evaluation report, i.e. it links dynamic output from simulations with observed data and static text modules and defines desired figures and tables

# OSP Repository Landscape

## Working repositories

- **Model repositories** for single PBPK substance models: **<Substance>-Model**. The repository contains the PBPK substance model in form of its snapshot along with its evaluation plan (and static text modules) and serves for their development, maintenance and releases.
- (Dependent intermediate) model repositories **needed for specific qualification scenarios**, e.g. model snapshot files containing DDI simulations of two interacting compounds (**<Substance1>-<Substance2>-DDI**) or pediatric simulations (**<Substance>-Pediatric**).
- **Qualification repositories** for specific qualification purposes: **Qualification-<intended purpose>**. The repository contains the qualification plan (and static text modules) and serves for its development, maintenance and releases.
- The **OSP database for observed PK data**: [\*\*Database-for-observed-data\*\*](#). It contains PK data from publicly available sources for the use in PBPK simulations. The database integrates information from published clinical studies about study designs, **statistics of PK parameters** (area under the plasma concentration-time curve (AUC), peak plasma concentration ( $C_{max}$ ), etc.), **digitized concentration-time profiles and DDI records** (AUC ratios (AUCR) and  $C_{max}$  ratios ( $C_{max}R$ )). Respective data can easily be integrated into PK-Sim® or used in the context of qualifications. **The OSP database for observed PK data has been released and already contains in its current version 1.2 more than 1000 concentration-time profiles from more than 300 publications.**

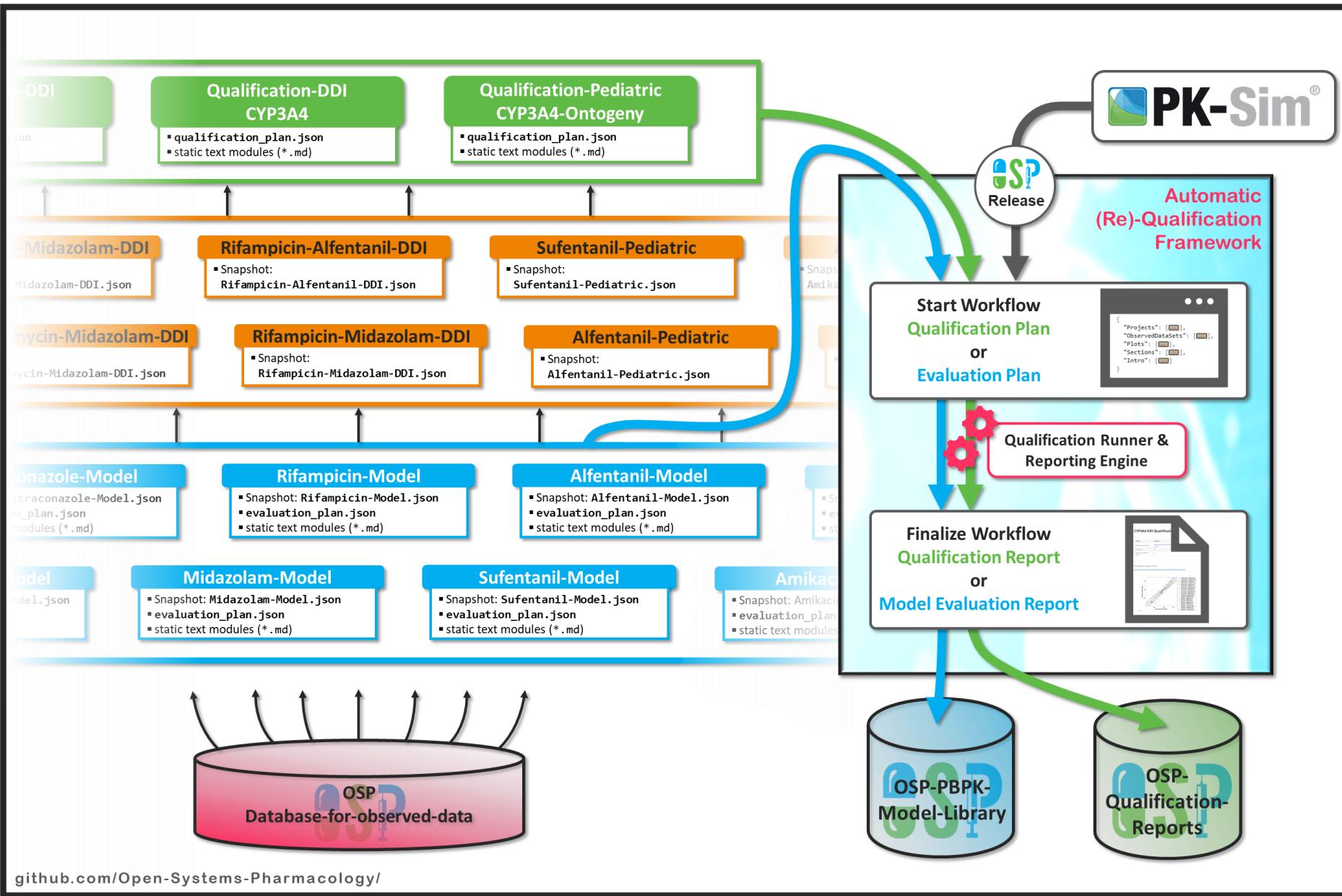
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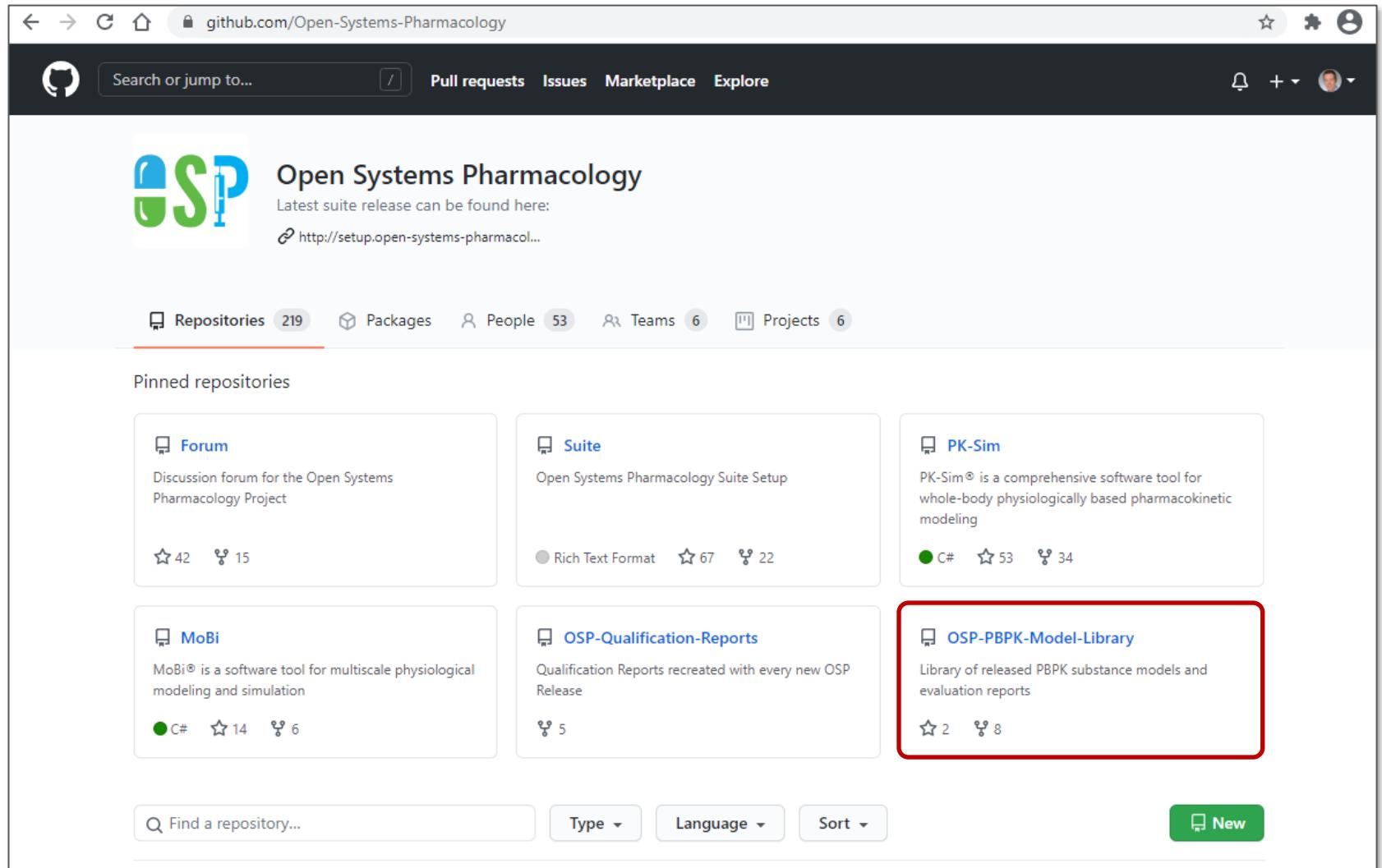
## Top level repositories

- The **[OSP-PBPK-Model-Library](#)** constitutes a special repository comprising the officially released PBPK substance models for the use in PK-Sim. These models are published along with a respective model evaluation report.
- The **[OSP-Qualification-Reports](#)** constitutes another special repository that contains the officially released qualifications of the PK-Sim platform (as qualification reports) for specific intended purposes.



from Frechen et al. CPT Pharmacometrics Syst Pharmacol . 2021. Accepted.

# GitHub Tour



github.com/Open-Systems-Pharmacology

Search or jump to... Pull requests Issues Marketplace Explore

Open Systems Pharmacology  
Latest suite release can be found here:  
<http://setup.open-systems-pharmacology.org>

Repositories 219 Packages People 53 Teams 6 Projects 6

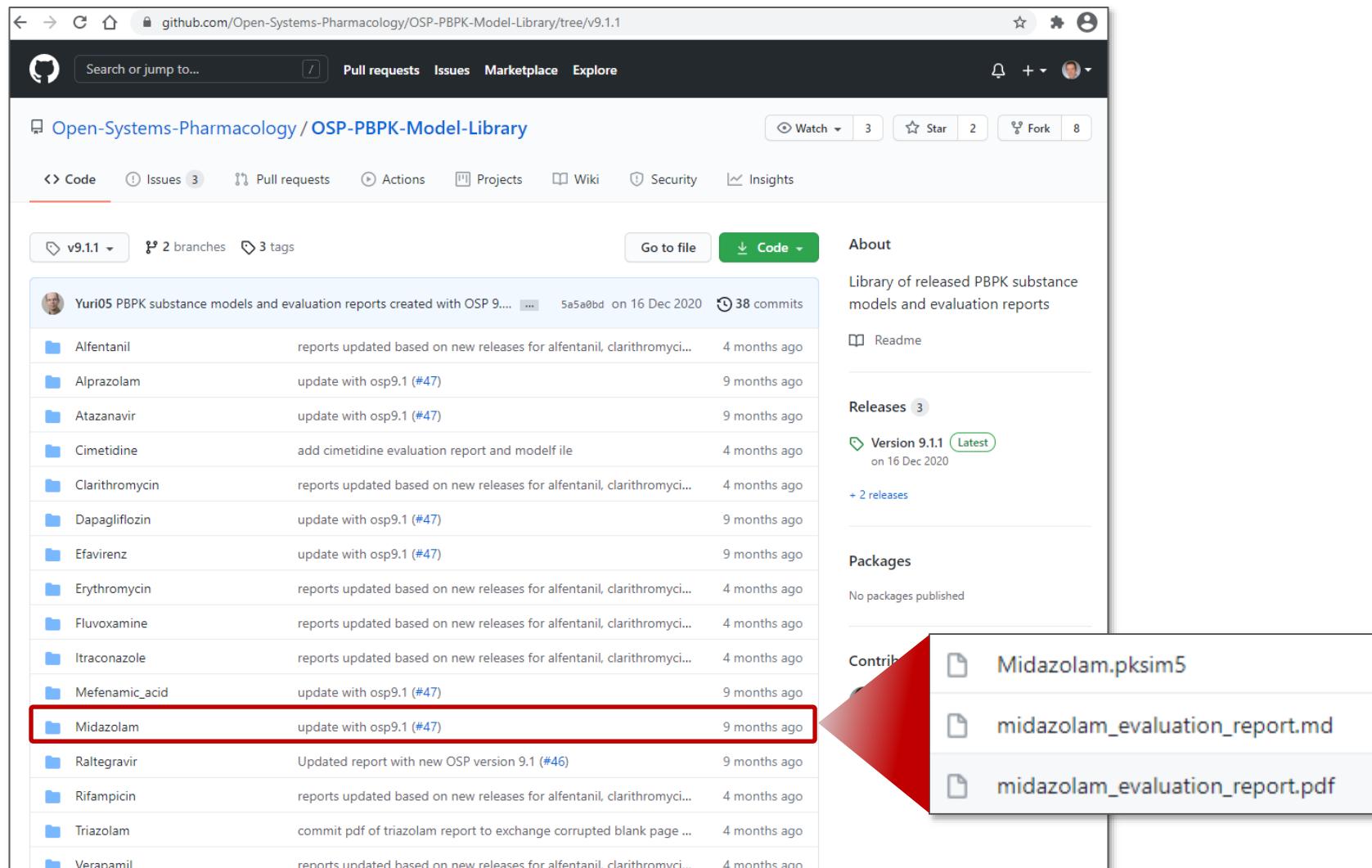
Pinned repositories

- Forum**  
Discussion forum for the Open Systems Pharmacology Project  
42 stars, 15 forks
- Suite**  
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- OSP-Qualification-Reports**  
Qualification Reports recreated with every new OSP Release  
5 forks
- OSP-PBPK-Model-Library**  
Library of released PBPK substance models and evaluation reports  
2 stars, 8 forks

Find a repository... Type Language Sort New

# OSP-PBPK-Model-Library

Release 9.1.1



The screenshot shows the GitHub repository page for the OSP-PBPK-Model-Library. The repository has 2 branches and 3 tags. The v9.1.1 tag is selected. The repository has 38 commits. A red box highlights the commit for Midazolam, which was updated with osp9.1 (#47) 9 months ago. To the right, a red arrow points to a callout box containing three files: Midazolam.pksim5, midazolam\_evaluation\_report.md, and midazolam\_evaluation\_report.pdf.

Commit	Description	Date
Alfentanil	reports updated based on new releases for alfentanil, clarithromycin...	4 months ago
Alprazolam	update with osp9.1 (#47)	9 months ago
Atazanavir	update with osp9.1 (#47)	9 months ago
Cimetidine	add cimetidine evaluation report and model file	4 months ago
Clarithromycin	reports updated based on new releases for alfentanil, clarithromycin...	4 months ago
Dapagliflozin	update with osp9.1 (#47)	9 months ago
Efavirenz	update with osp9.1 (#47)	9 months ago
Erythromycin	reports updated based on new releases for alfentanil, clarithromycin...	4 months ago
Fluvoxamine	reports updated based on new releases for alfentanil, clarithromycin...	4 months ago
Itraconazole	reports updated based on new releases for alfentanil, clarithromycin...	4 months ago
Mefenamic_acid	update with osp9.1 (#47)	9 months ago
<b>Midazolam</b>	<b>update with osp9.1 (#47)</b>	<b>9 months ago</b>
Raltegravir	Updated report with new OSP version 9.1 (#46)	9 months ago
Rifampicin	reports updated based on new releases for alfentanil, clarithromycin...	4 months ago
Triazolam	commit pdf of triazolam report to exchange corrupted blank page ...	4 months ago
Verapamil	reports updated based on new releases for alfentanil, clarithromycin...	4 months ago

# Exemplary evaluation report

[github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/blob/v9.1.1/Midazolam/midazolam\\_eval...](https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/blob/v9.1.1/Midazolam/midazolam_eval...)

604 lines (382 sloc) | 58.6 KB

Raw Blame

## Building and evaluation of a PBPK model for Midazolam in healthy adults

Version	1.0-OSP9.1
based on Model Snapshot and Evaluation Plan	<a href="https://github.com/Open-Systems-Pharmacology/Midazolam-Model/releases/tag/v1.0">https://github.com/Open-Systems-Pharmacology/Midazolam-Model/releases/tag/v1.0</a>
OSP Version	9.1
Qualification Framework Version	2.2

This evaluation report and the corresponding PK-Sim project file are filed at:

<https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/>

## Table of Contents

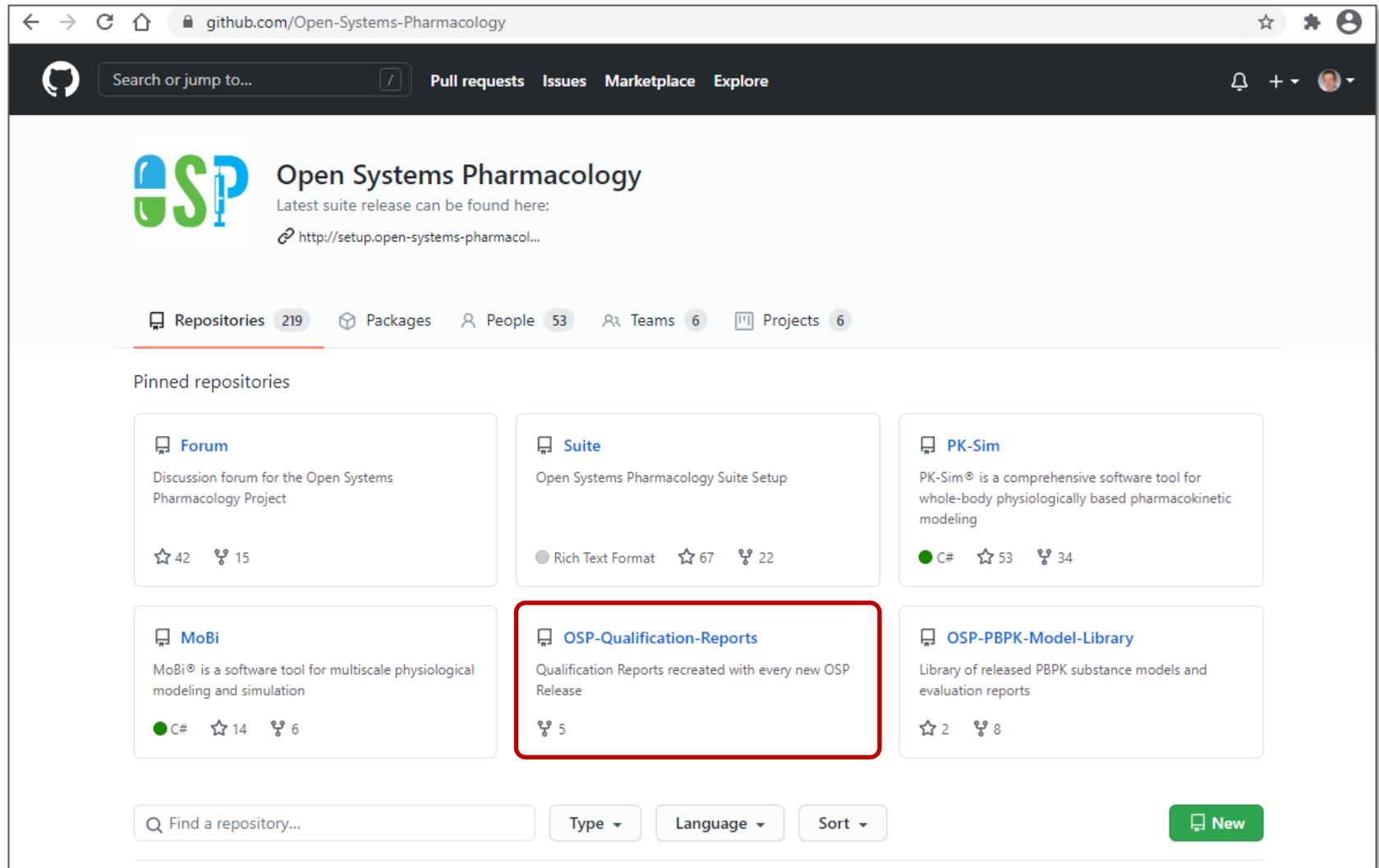
- 1 Introduction
- 2 Methods
  - 2.1 Modeling Strategy
  - 2.2 Data
  - 2.3 Model Parameters and Assumptions
- 3 Results and Discussion
  - 3.1 Final input parameters
  - 3.2 Diagnostics Plots
  - 3.3 Concentration-Time Profiles
    - 3.3.1 Model Building
    - 3.3.2 Model Verification
- 4 Conclusion
- 5 References

## 1 Introduction

Midazolam is a widely-used sedative, approved as premedication before surgical interventions. It is almost exclusively metabolized by CYP3A4 making it a sensitive probe and victim drug for the investigation of CYP3A4 activity *in vivo*. Midazolam shows substantial first pass metabolism resulting in a bioavailability of under 50%. Less than 1% of a midazolam dose is excreted unchanged in urine.

The herein presented model represents an update of the midazolam model published by Hanke et al. ([Hanke 2018](#)). The model has been developed using in particular published pharmacokinetic clinical data by Hohmann et al. ([Hohmann 2015](#)), Hyland et al. 2009 ([Hyland 2009](#)) and Thummel et al. 1996 ([Thummel 1996](#)). It has then been evaluated by comparing observed data to simulations of a large number of clinical studies covering a dose range of 0.05 mg/kg to 20 mg after intravenous and oral administrations. Furthermore, it has been evaluated within a

# GitHub Tour



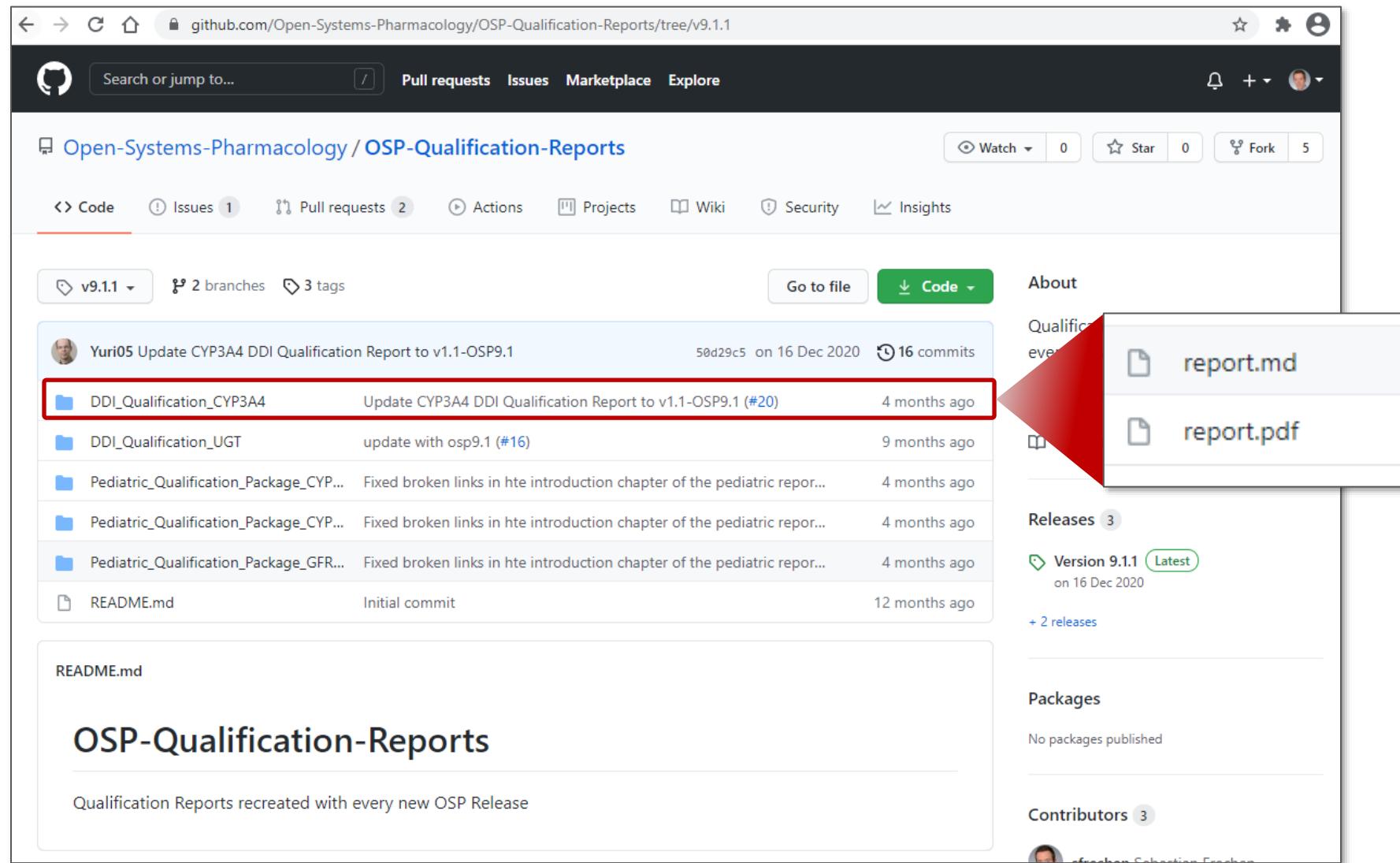
The screenshot shows the GitHub profile page for the organization "Open Systems Pharmacology". The page includes the organization's logo, a search bar, and navigation links for Pull requests, Issues, Marketplace, and Explore. Below this, there is a section for pinned repositories, which includes the following items:

- Forum**: Discussion forum for the Open Systems Pharmacology Project. 42 stars, 15 forks.
- Suite**: Open Systems Pharmacology Suite Setup. Rich Text Format, 67 stars, 22 forks.
- PK-Sim**: PK-Sim® is a comprehensive software tool for whole-body physiologically based pharmacokinetic modeling. C#, 53 stars, 34 forks.
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- OSP-PBPK-Model-Library**: Library of released PBPK substance models and evaluation reports. 2 stars, 8 forks.

At the bottom of the pinned repositories section, there is a red rectangular box highlighting the "OSP-Qualification-Reports" repository. Below the pinned repositories, there is a search bar and buttons for Type, Language, Sort, and a green "New" button.

# OSP-Qualification-Reports

Release 9.1.1



The screenshot shows the GitHub repository page for `OSP-Qualification-Reports`. The repository has 5 forks and 0 stars. The `v9.1.1` release is selected, showing 2 branches and 3 tags. The commit history for `v9.1.1` includes:

- Yuri05 Update CYP3A4 DDI Qualification Report to v1.1-OSP9.1** (50d29c5, 16 Dec 2020) - 16 commits
  - DDI\_Qualification\_CYP3A4** (Update CYP3A4 DDI Qualification Report to v1.1-OSP9.1 (#20)) - 4 months ago
  - DDI\_Qualification\_UGT** (update with osp9.1 (#16)) - 9 months ago
  - Pediatric\_Qualification\_Package\_CYP...** (Fixed broken links in hte introduction chapter of the pediatric repor...) - 4 months ago
  - Pediatric\_Qualification\_Package\_CYP...** (Fixed broken links in hte introduction chapter of the pediatric repor...) - 4 months ago
  - Pediatric\_Qualification\_Package\_GFR...** (Fixed broken links in hte introduction chapter of the pediatric repor...) - 4 months ago
  - README.md** (Initial commit) - 12 months ago
- READMD.md**

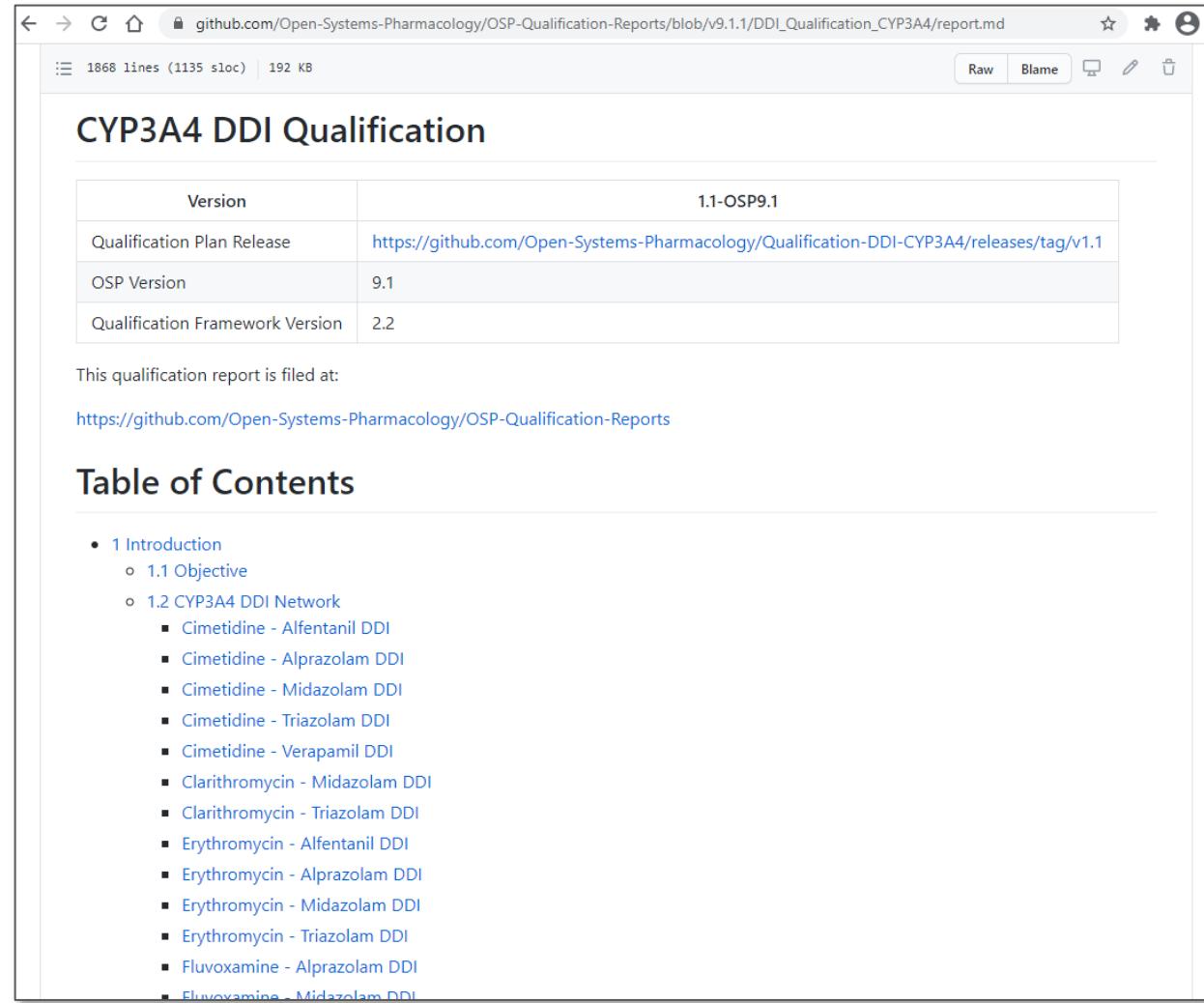
The `README.md` file contains the following content:

```
OSP-Qualification-Reports

Qualification Reports recreated with every new OSP Release
```

A red arrow points from the `report.md` file in the dropdown menu to the `report.pdf` file, indicating they are related documents.

# Exemplary qualification report



The screenshot shows a GitHub page for a file named `report.md` located at [https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports/blob/v9.1.1/DDI\\_Qualification\\_CYP3A4/report.md](https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports/blob/v9.1.1/DDI_Qualification_CYP3A4/report.md). The page title is "CYP3A4 DDI Qualification". It contains a table with version information:

Version	1.1-OSP9.1
Qualification Plan Release	<a href="https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4/releases/tag/v1.1">https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4/releases/tag/v1.1</a>
OSP Version	9.1
Qualification Framework Version	2.2

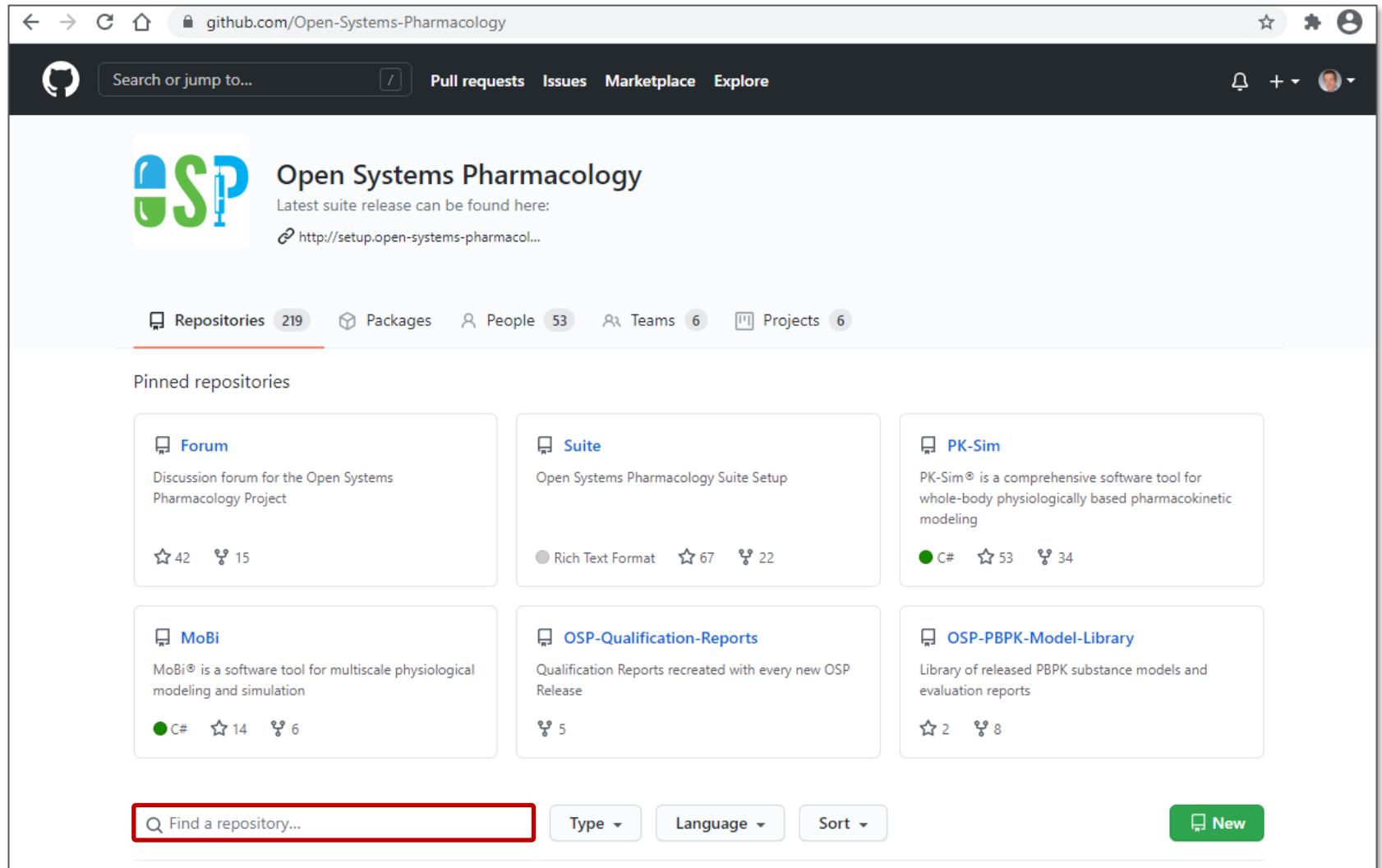
This qualification report is filed at:

<https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports>

## Table of Contents

- 1 Introduction
  - 1.1 Objective
  - 1.2 CYP3A4 DDI Network
    - Cimetidine - Alfentanil DDI
    - Cimetidine - Alprazolam DDI
    - Cimetidine - Midazolam DDI
    - Cimetidine - Triazolam DDI
    - Cimetidine - Verapamil DDI
    - Clarithromycin - Midazolam DDI
    - Clarithromycin - Triazolam DDI
    - Erythromycin - Alfentanil DDI
    - Erythromycin - Alprazolam DDI
    - Erythromycin - Midazolam DDI
    - Erythromycin - Triazolam DDI
    - Fluvoxamine - Alprazolam DDI
    - Fluvoxamine - Midazolam DDI

# GitHub Tour



github.com/Open-Systems-Pharmacology

Search or jump to... Pull requests Issues Marketplace Explore

Open Systems Pharmacology  
Latest suite release can be found here:  
<http://setup.open-systems-pharmacology.org>

Repositories 219 Packages People 53 Teams 6 Projects 6

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Find a repository... Type Language Sort New

github.com/Open-Systems-Pharmacology/Midazolam-Model

Pull requests Issues Marketplace Explore

Open-Systems-Pharmacology / Midazolam-Model

Code Issues Pull requests Marketplace

master 1 branch 2 tags

sfrechen links to references fixed ...

Evaluation

Midazolam-Model.json

README.md

README.md

## Midazolam-Model

Whole-body PBPK model of midazolam

CN1C=NC2=C1C(Cl)=CC(F)=CC=C2

This repository contains:

- a PK-Sim snapshot (\*.json) file
- static content (e.g. text blocks,
- an evaluation plan (evaluation-static text blocks to display the

Itraconazole-Midazolam-DDI

Modeling of published clinical Itraconazole-Midazolam-DDI studies for m...

Within this repository, we distribute a PK-Sim snapshot file containing sim...

Itraconazole-Midazolam-DDI, including the respective observed data digit...

The reference model repositories can be found here:

- Itraconazole OSP PBPK model
- Midazolam OSP PBPK model

Code of conduct

Everyone interacting in the Open Systems Pharmacology community (cod...

github.com/Open-Systems-Pharmacology/Itraconazole-Midazolam-DDI

Pull requests Issues Marketplace

Open-Systems-Pharmacology / Itraconazole-Midazolam-DDI

Code Issues Pull requests Actions Projects Wiki Security Insights Settings

master 1 branch 2 tags Go to file Add file Code

TeeVenDick Fix typo (#12) fdb6e42 on 11 Jan 88 commits

.github/workflows Add spell check action (#11) 3 months ago

Qualification Fix typo (#12) 3 months ago

.spellcheck.yml Add spell check action (#11) 3 months ago

README.md update 11 months ago

README.md

## Qualification-DDI-CYP3A4

This repository contains a qualification plan (*qualification\_plan.json*) including references to respective model snapshots and static content (e.g. text blocks, \*.md files) to produce a qualification report evaluating the ability to perform simulations with the intended purpose to predict cytochrome P450 3A4 (CYP3A4)-mediated drug-drug interactions (DDI) of the PBPK platform PK-Sim (as part of the open systems pharmacology (OSP) suite).

The latest release of the qualification plan and the static content can be found [here](#).

The latest release of the qualification report can be found [here](#).

To demonstrate the level of confidence, the predictive performance of the platform for this indented

Releases 2

Qualification Plan Release... Latest on 16 Dec 2020 + 1 release

Packages

No packages published Publish your first package

Contributors 5

<Substance1>-<Substance2>-DDI Repository

Qualification Plan Repository

# Qualification Framework Summary

- agile and sustainable technical framework for automatic PBPK platform (re-)qualification of PK-Sim
- embedded in the open-source and open-science GitHub landscape of OSP
- enables efficient assessment of the current predictive performance of the platform for all kinds of intended purposes (e.g. DDI applications, pediatric translations, etc.)
- provides full transparency and traceability for all stakeholders
- A detailed technical *how-to* of the whole workflow can be found in the OSP documentation:  
<https://docs.open-systems-pharmacology.org/shared-tools-and-example-workflows/qualification>



Platform Qualification Showcase:  
**Predicting CYP3A4-mediated DDI**

# Objective and Set-up

## Objective:

- assess the platform's overall predictive performance for the intended purpose of predicting CYP3A4-mediated DDI

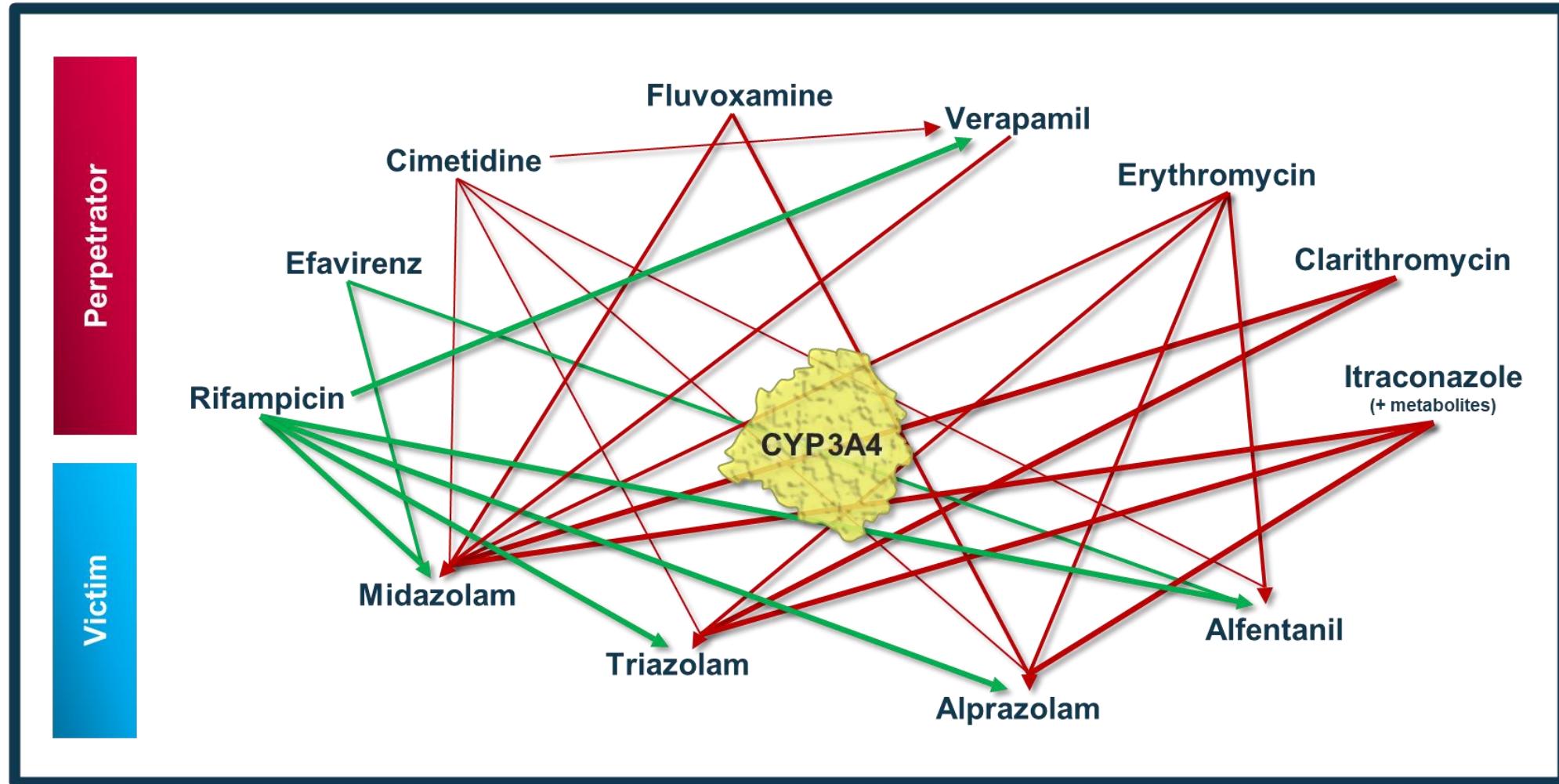
## Set-up:

- Specification of a set of PBPK substance models of:
  - index perpetrators, covering the range from strong CYP3A4 induction to strong inhibition
  - CYP3A4 DDI victim drugs was specified to set up a DDI modeling network.
- mutual evaluation of all models to verify the perpetrator's and victim's properties with regard to CYP3A4 modulation and metabolism
- evaluation performed by comparison of simulations against observations of a comprehensive qualification dataset of published clinical DDI studies

# Idea, set-up, objective

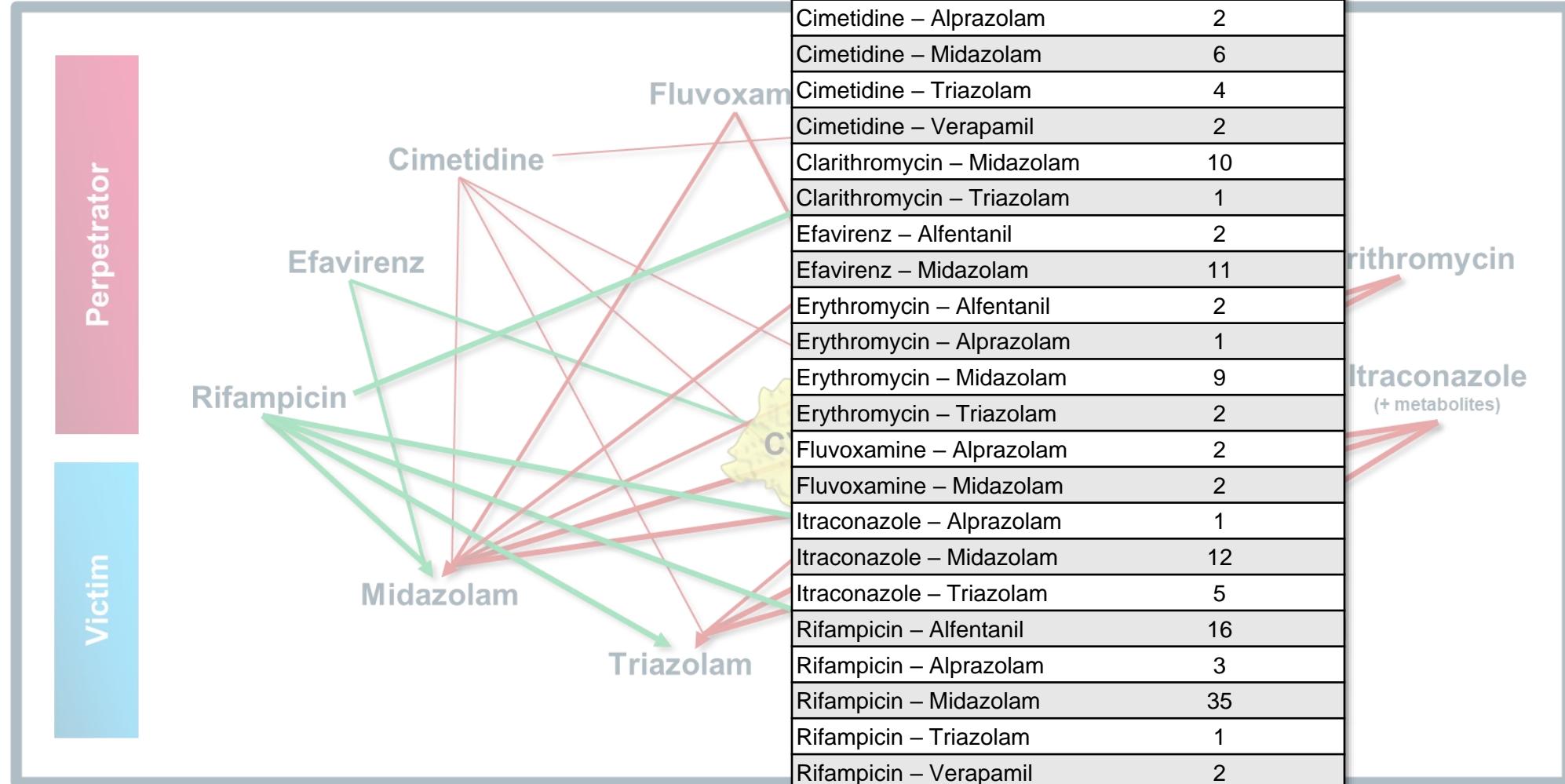
- Specification of a set of PBPK substance models of:
  - index perpetrators, covering the range from strong CYP3A4 induction to strong inhibition
  - CYP3A4 DDI victim drugs was specified to set up a DDI modeling network.
- Each model was mutually evaluated to verify the perpetrator's and victim's properties **with regard to CYP3A4 modulation and metabolism**, respectively, by comparing simulations against observations of a comprehensive qualification dataset of published clinical DDI studies.
- **Objective:** to assess the platform's overall predictive performance for the intended purpose of predicting CYP3A4-mediated DDI.

# DDI Network CYP3A4



from Frechen et al. CPT Pharmacometrics Syst Pharmacol . 2021. Accepted.

# DDI Network CYP3A4



# Results

- All presented PBPK models represent whole-body PBPK models, which allow dynamic DDI simulations in organs expressing CYP3A4.
- All models have been released along with detailed model evaluation reports with the current OSP version 9.1 and are freely accessible:  
<https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/releases/tag/v9.1.1>
- Simulations were compared against 135 observations of the qualification dataset of published clinical DDI studies. Detailed information on the respective study designs is outlined in the released qualification report.
- The current underlying qualification plan has been released as **version 1.1**:  
<https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4/releases/tag/v1.1>
- The qualification report was created for the current OSP version 9.1 and has been released as the corresponding **version 1.1-OSP9.1**:  
[https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports/tree/v9.1.1/DDI\\_Qualification\\_CYP3A4](https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports/tree/v9.1.1/DDI_Qualification_CYP3A4)

# Excerpts from the Qualification-Report I

- Details on studies

## Itraconazole - Midazolam DDI

The release of the snapshot containing the respective simulations can be found here: <https://github.com/Open-Systems-Pharmacology/Itraconazole-Midazolam-DDI/releases/tag/v1.1>

The itraconazole / midazolam interaction was evaluated using seven clinical DDI studies including 12 different clinical settings (Ahonen 1995, Backman 1998, Olkkola 1994, Olkkola 1996, Prueksaritanont 2017, Templeton 2010, Yu 2004).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
50	CYP3A4	Itraconazole / midazolam	Itraconazole: 100 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, simultaneous with 4 <sup>th</sup> itraconazole dose		Ahonen 1995
58	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 2 hours after 4 <sup>th</sup> itraconazole dose	Midazolam simulated as 15 mg for comparability to control phase, in which a 15 mg dose was given.	Backman 1998
59	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 4 days after 4 <sup>th</sup> itraconazole dose	Midazolam simulated as 15 mg for comparability to control phase, in which a 15 mg dose was given.	Backman 1998
370	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 1 hours after 4 <sup>th</sup> itraconazole dose		Olkkola 1994
377	CYP3A4	Itraconazole /	Itraconazole: 200 mg po once daily (6 doses, capsule fasted) Midazolam: 7.5 mg po single		Olkkola 1996

# Excerpts from the Qualification-Report I

- Details on studies
- More details accessible via the *DataID* in the *Database for observed data*

<https://github.com/Open-Systems-Pharmacology/Database-for-observed-data>

## Itraconazole - Midazolam DDI

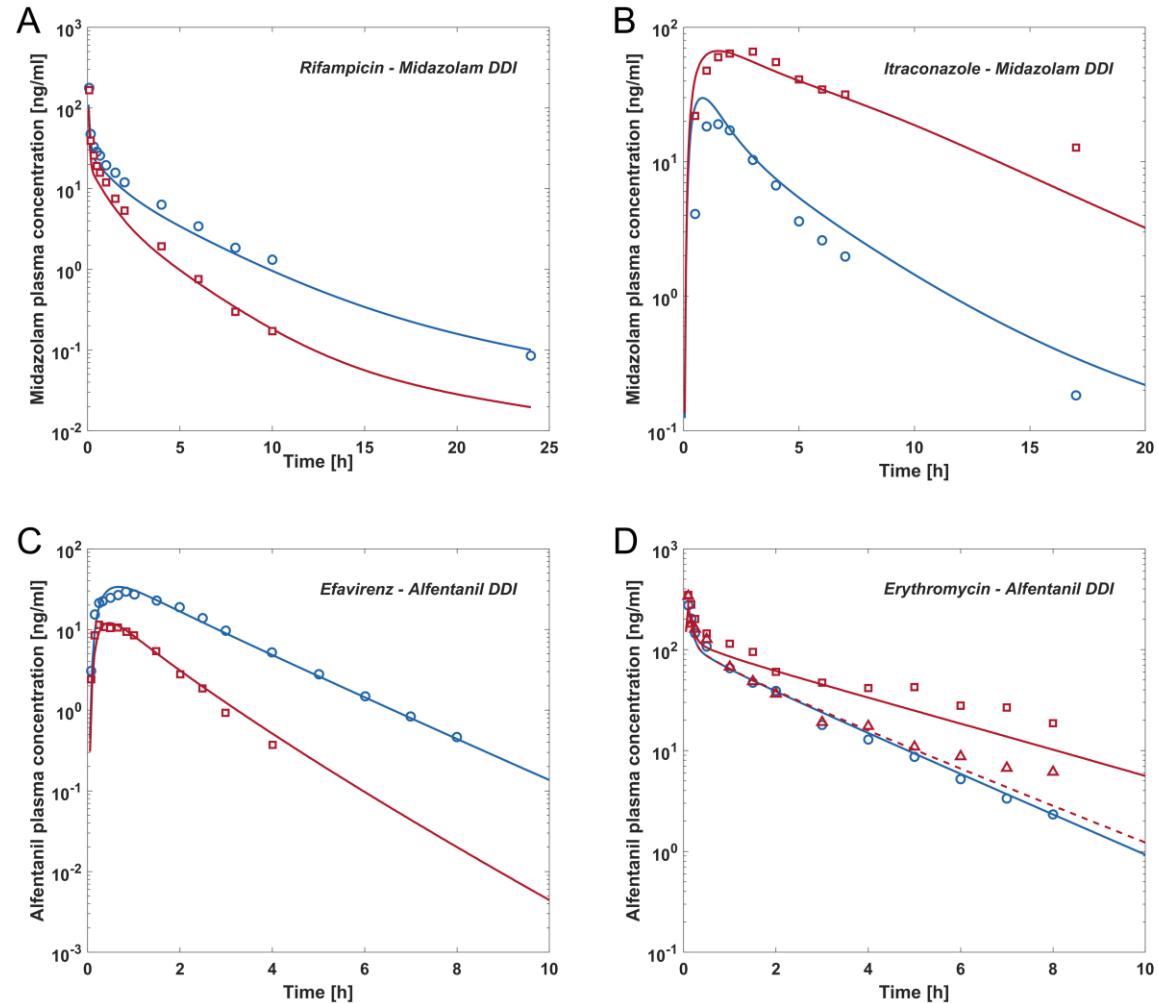
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377	CYP3A4	Itraconazole /	Itraconazole: 200 mg po once daily (6 doses, capsule fasted) Midazolam: 7.5 mg po single		Olkkola 1996

# Excerpts from the Qualification-Report II

- Concentration-time profile plots for all sets of simulation and observed data

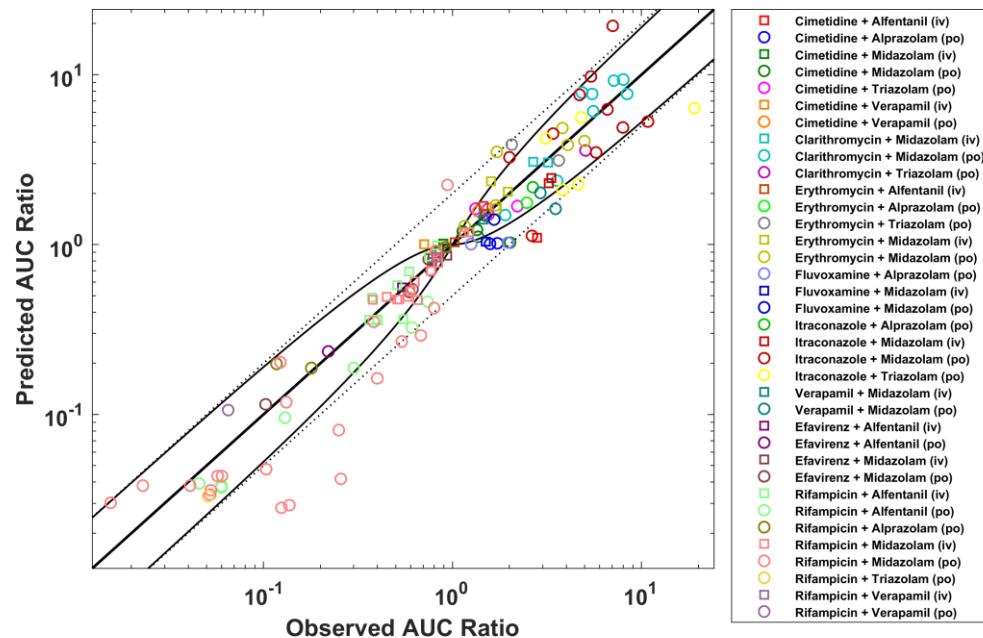


from Frechen et al. CPT Pharmacometrics Syst Pharmacol . 2021. Accepted.

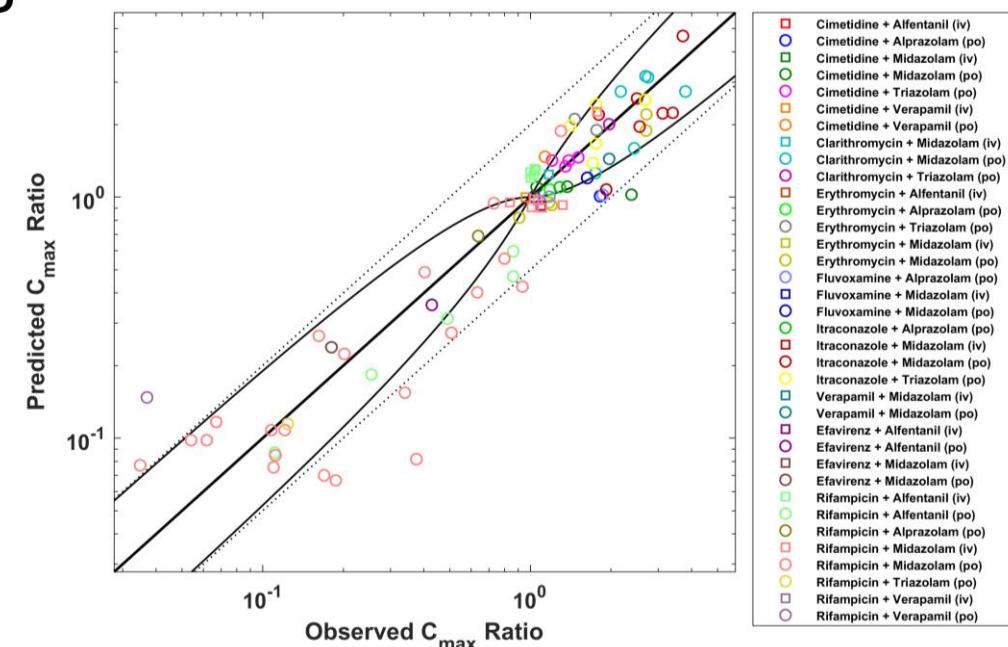
# Excerpts from the Qualification-Report III

- Predicted vs. observed plots
- also available in the report: categorized **by type of DDI mechanism** (competitive inhibition, mechanism-based inactivation and induction) and **by compound** of the network

**A**



**B**



from Frechen et al. CPT Pharmacometrics Syst Pharmacol . 2021. Accepted.

# Excerpts from the Qualification-Report IV

- Numerical summaries
- also available in the report: categorized **by type of DDI mechanism** (competitive inhibition, mechanism-based inactivation and induction) and **by compound** of the network

GMFE (AUCR) = 1.39

GMFE (C<sub>MAX</sub>R) = 1.37

Geometric mean fold error (GMFE)

$$10^{\frac{\sum |\log(\frac{Pred}{Obs})|}{n}}$$

	AUC	Number	Ratio [%]
Points total	135	-	
Points within Guest et al.*	99	73.3333	
Points within 2-fold	118	87.4074	

	CMAX	Number	Ratio [%]
Points total	88	-	
Points within Guest et al.*	49	55.6818	
Points within 2-fold	80	90.9091	

\* Guest EJ, et al. Drug Metab Dispos. 2011 Feb;39(2):170-3

# Summary

- The overall prediction accuracy in terms of CYP3A4-mediated DDI is comparable with recent reports in literature.
  - Marsousi et al. (Simcyp™ software): analysis of 74 CYP3A4-mediated DDI studies with a GMFE for AUCR of approximately 1.5
  - EMA (summary of current drug interaction guidance): accepted platform qualification of the purpose to predict time-dependent inhibition (i.e. MBI) of CYP3A4 with a GMFE for AUCR of approximately 1.4
- The qualification package demonstrates that sponsors can use PK-Sim® - *more specifically PK-Sim® version 9.1* - to successfully evaluate CYP3A4-mediated DDI in clinically untested scenarios for new investigational drugs either as enzyme substrate or perpetrator within the presented compound network.

Marsousi N, et al. Biopharmaceutics & drug disposition. 2018;39(1): 3-17.  
Cole S, et al. Drug metabolism and pharmacokinetics. 2020;35(1): 2-11.

# Conclusion

- An agile and sustainable technical framework for automatic PBPK platform (re-)qualification of PK-Sim® has been developed and embedded in the open-source and open-science GitHub landscape of OSP. The presented approach
  - enables an efficient assessment of the current predictive performance of the platform for all kinds of intended purposes (e.g. DDI applications, pediatric translations, etc.)
  - provides full transparency and traceability for all stakeholders including regulatory agencies.
- To demonstrate the power and versatility of the qualification framework, the qualification of PK-Sim® for simulating CYP3A4-mediated DDI was successfully developed and released as a showcase example for future platform qualifications of various intended purposes.

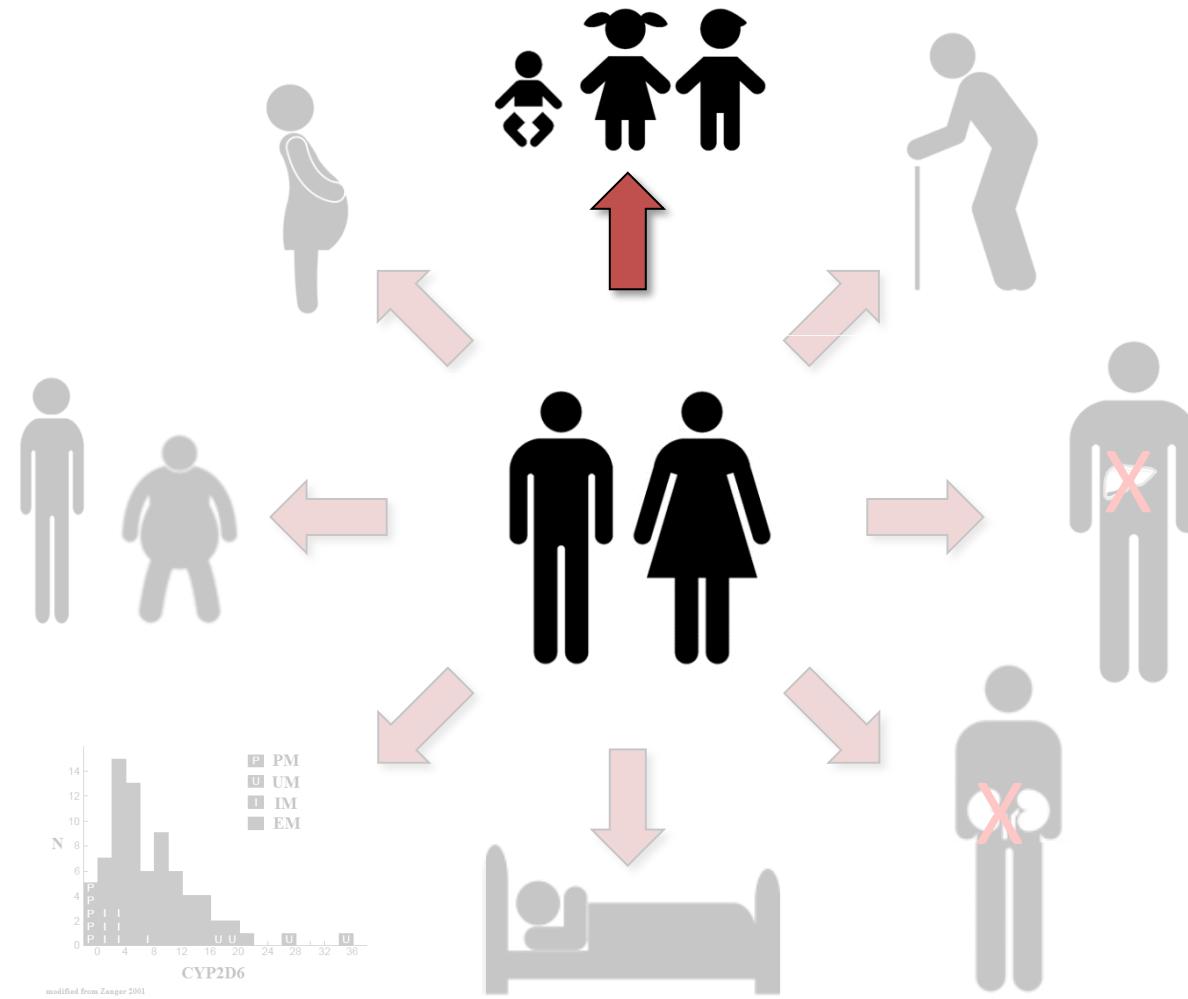


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## Pediatric PBPK Applications

Ibrahim Ince, Bayer AG

# Application of PBPK M&S in Specific populations



# Application of PBPK in Pediatric Research

- During drug development, the question **how to dose pediatric patients** comes up during the early clinical development in adults
- PBPK modeling can then be used to **prospectively** establish the relationship between dose and exposure that is expected in children of different ages.
- The standard requirements for extrapolating an adult PBPK model of a typical small molecule drug candidate to children are
  - a good understanding of the **ADME** behavior of the drug candidate in adults, in particular mass-balance information
  - the availability of known **ontogeny information** of the processes relevant for ADME, especially the ontogeny of the involved clearance processes

- In cases where multiple pathways contribute to the metabolism and elimination of the drug candidate, it might still be acceptable, if ontogeny functions for individual pathways are not available, if the fractional contribution of the unknown process to the overall clearance is low.
- In this case the impact of this lack of earlier knowledge on the dose-exposure relation should be assessed by means of a sensitivity analysis considering the best- and worst-case scenarios with respect to the rate at which developmental changes can reasonably occur.

# PBPK modeling in adults and translation to children in Open Systems Pharmacology (PK-Sim / MoBi)

## Building blocks of a PBPK model for adults

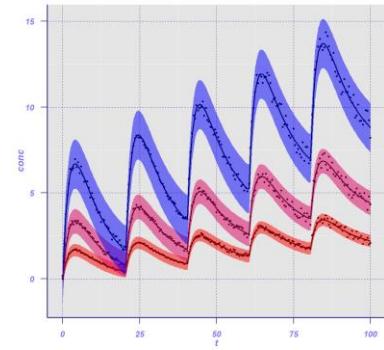
### Drug properties



### Organism properties



### Study protocol and formulation properties



## Building blocks of a PBPK model for children

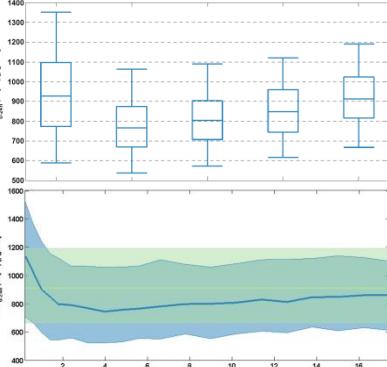
### Drug properties



### Organism properties



### Study protocol and formulation properties



### Physicochemical properties

- Lipophilicity
- Molecular weight
- pKa/pKb

### Anatomy & physiology

- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

### Drug-biology interaction

- Fraction unbound
- Partition coefficients
- Mass Balance

- Fractional CL contributions
- Permeability
- Active processes ( $K_m$ ,  $V_{max}$ )

### Formulation

(empirical or mechanistic dissolution function)

### Administration protocol

(dose and dosing regimen)

### Special events

(food intake, exercise, EHC)

### Physicochemical properties

- Lipophilicity
- Molecular weight
- pKa/pKb

### Age-dependent changes in anatomy & physiology

### Resulting age-dependent changes in drug-biology interaction

### Modified formulations

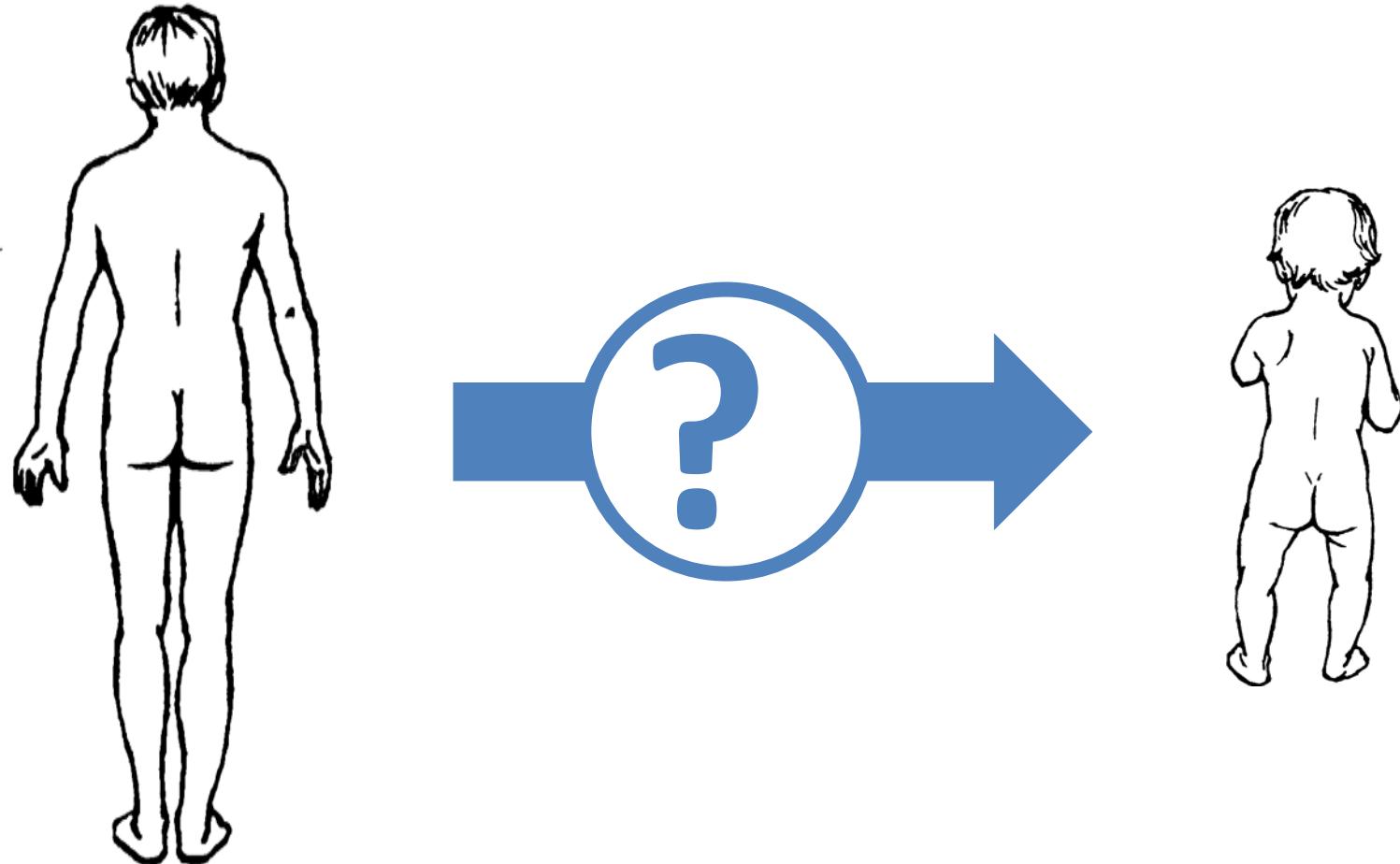
(e.g. minitablets, syrup)

### Adjusted administration protocol

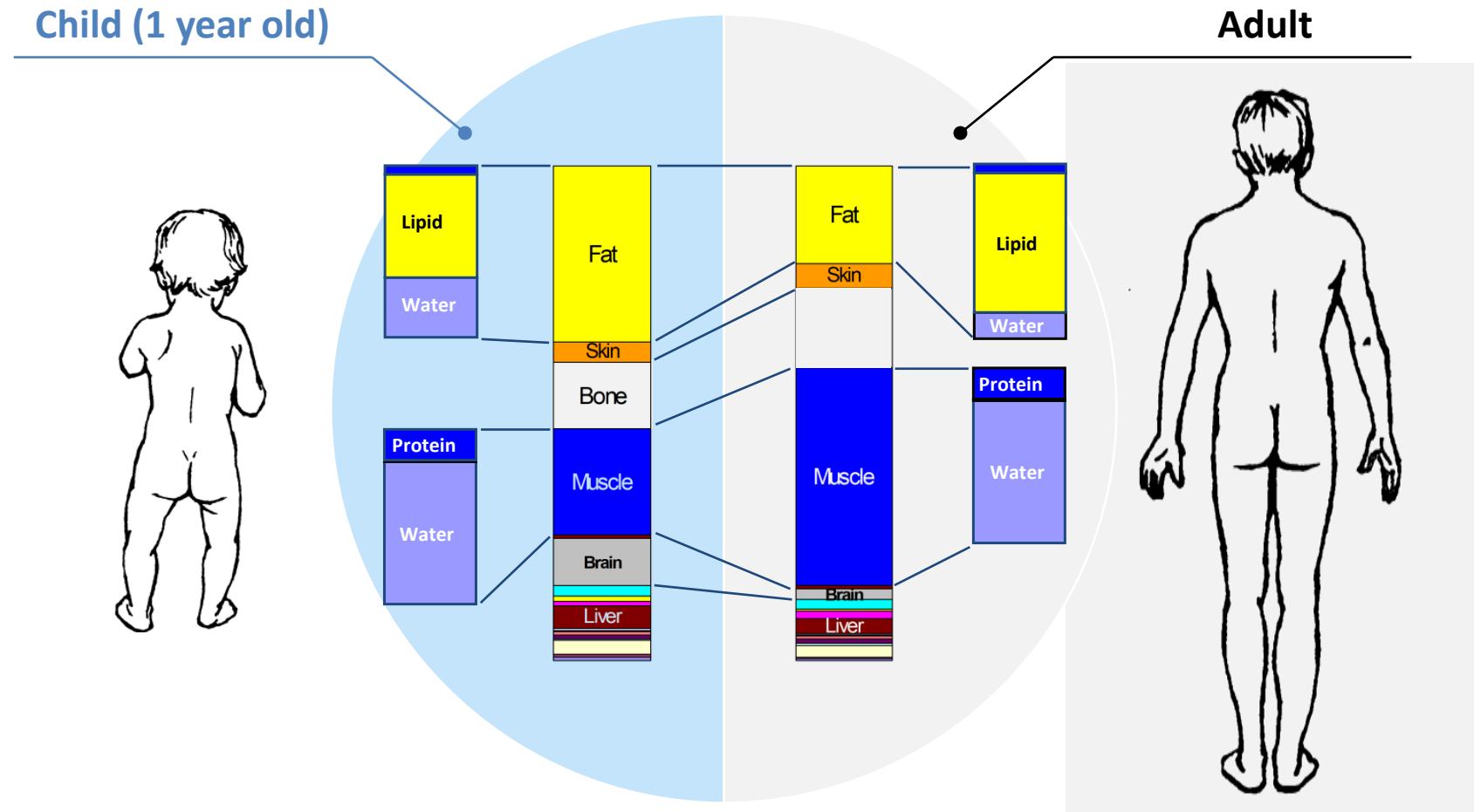
(e.g. mg/kg dosing)

### Different special events

# Bridging from Adults to Children – What Information Do We Need?

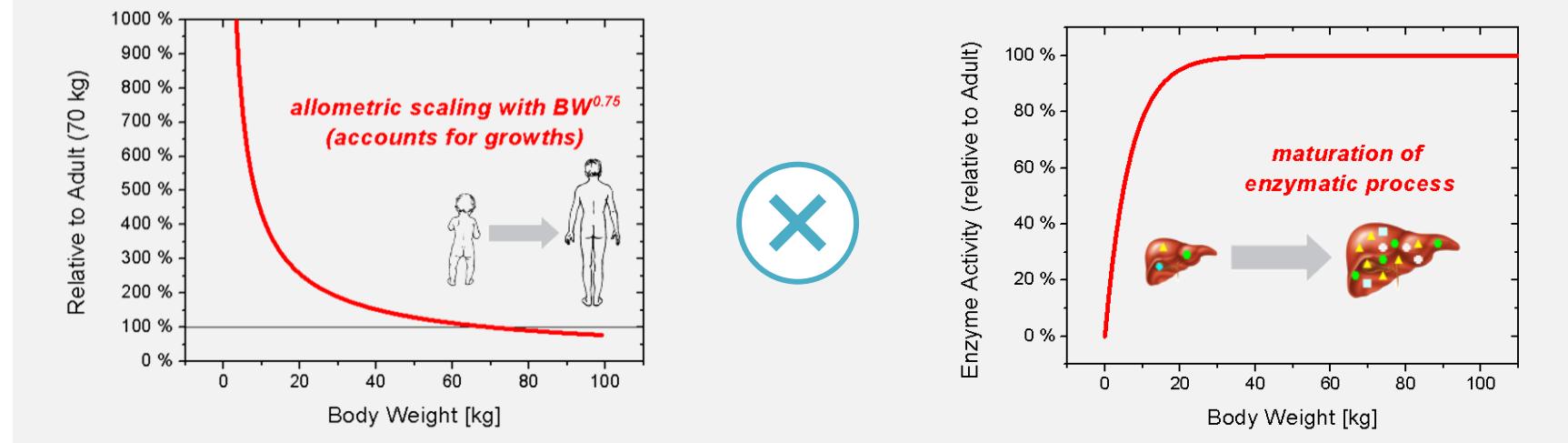


# Age Dependence of Body Composition



Edginton et al., *Clin. Pharmacokin.* **45**(10), 1013-34 (2006)

# Age Dependence of Clearance Processes



# Established Ontogeny Functions

- Several articles have been published identifying the ontogeny of active processes such as phase 1 and phase 2 metabolizing enzymes and, to a lesser extent transporters, as well as passive processes such as GFR and plasma proteins
- Ontogeny information can originate from various sources
  - such as in the form of (semi)quantitative mRNA expression or *in vitro* activity data
  - by deconvolution of *in vivo* pharmacokinetic data in the case that information for all but 1 relevant clearance ontogeny is available
- A documentation of ontogenies that are included in PK-Sim is published in Github under OSP Suite Documentation:
  - <https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/master/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf>
  - This includes the origin of the input *in-vitro* data, the fit-results and ontogeny table used in pk-sim for phase 1 and phase 2 metabolizing enzymes and plasma proteins HSA and AAG

# Ontogeny Database

- Literature data to the age dependent expression of proteins influencing the ADME properties of drugs (enzymes, transporters, binding partners) were **(re)evaluated**
- **Data were fitted** using a maturation model based on a sigmoidal  $E_{max}$  model (corresponding to the Hill-equation):

$$A = \text{PMA}^n / (\text{A}_{0.5}^n + \text{PMA}^n)$$

**With:**

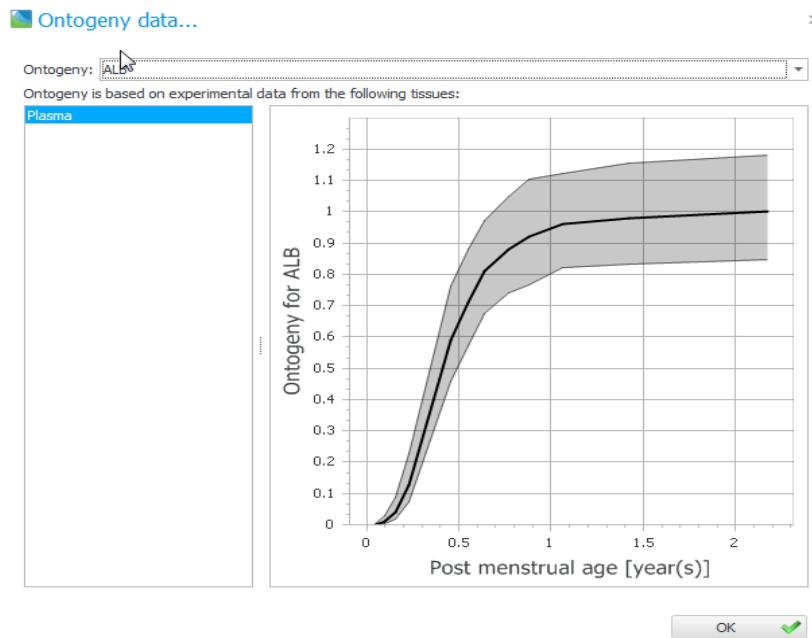
PMA = Postmenstrual age

A = Activity at PMA

$\text{A}_{0.5}$  = PMA at 50 % activity compared to adult

n = Hill coefficient

- Additionally, age-dependent variability of protein expression was **calculated**



# A novel approach to estimate ontogenies for PBPK applications

- More recently Mayer et al. (2018) introduced a novel approach to estimate ontogenies for PBPK applications
  - <https://www.page-meeting.org/default.asp?abstract=8583>
  - [https://www.page-meeting.org/pdf\\_assets/7901-2018\\_PAGE\\_Ontogeny OSP.pdf](https://www.page-meeting.org/pdf_assets/7901-2018_PAGE_Ontogeny OSP.pdf)
- This function allows to
  - cover the complete age range (including maturation and ageing) with one generic ontogeny function
  - Integrate individual and aggregated (e.g. mean and standard deviation) data.
- Markov Chain Monte Carlo (MCMC) methods, which allow the usage of aggregated data in combination with individual data, are used to estimate the parameters of a function describing the typical course of the ontogeny as well as the variability around it.
- It comprises a hill-function-like increase during the maturation phase and a hill-function-like decrease during the ageing phase
  - Currently applied for the ontogeny of AAG and will be used for new ontogenies.

# Predictive Pediatric Modeling and Simulation Using Ontogeny Information

	Pregnant	Preterm/Term newborn	Children	Elderly
<b>Known</b>				
<b>Less Known</b>				
<b>Needs elucidation</b>				
<b>Physiology: passive processes</b>	GFR Blood flows Organ sizes	GFR Blood flows Organ sizes	GFR Blood flows Organ sizes	GFR Blood flows Organ sizes
<b>Physiology: active processes</b>	CYP's UGT's transporters	CYP's UGT's transporters	CYP's UGT's transporters	CYP's UGT's transporters
<b>Pathophysiology</b>	e.g. Gestational hypertension / Pre-emclampsia	e.g. renal / hepatic impairment	e.g. renal / hepatic impairment	e.g. renal / hepatic impairment
<b>Therapeutic proteins</b>	Antibodies	Antibodies	Antibodies	Antibodies
<b>Therapeutic RNA gene expression modulators</b>	siRNA's, ASO's	siRNA's, ASO's	siRNA's, ASO's	siRNA's, ASO's
<b>Population specific</b>	Placental drug transfer and Fetal exposure	Absorption	Absorption	Mobility and Polypharmacotherapy

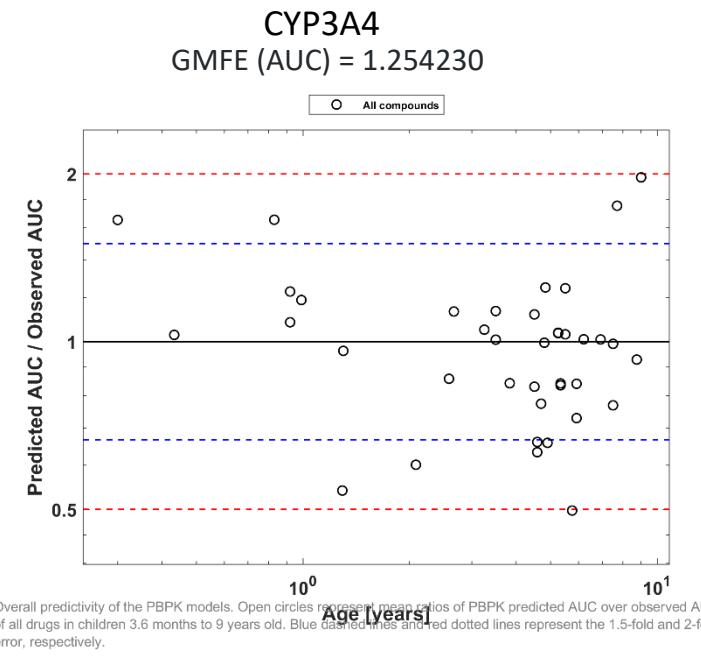
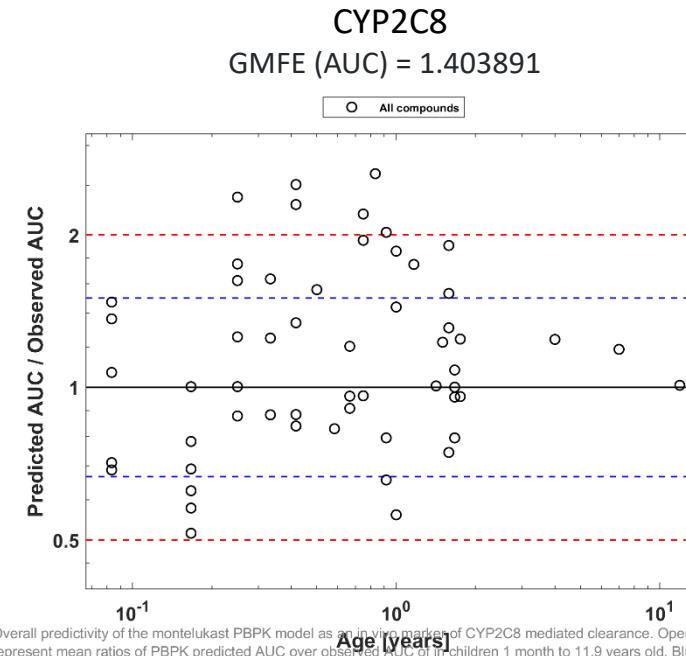
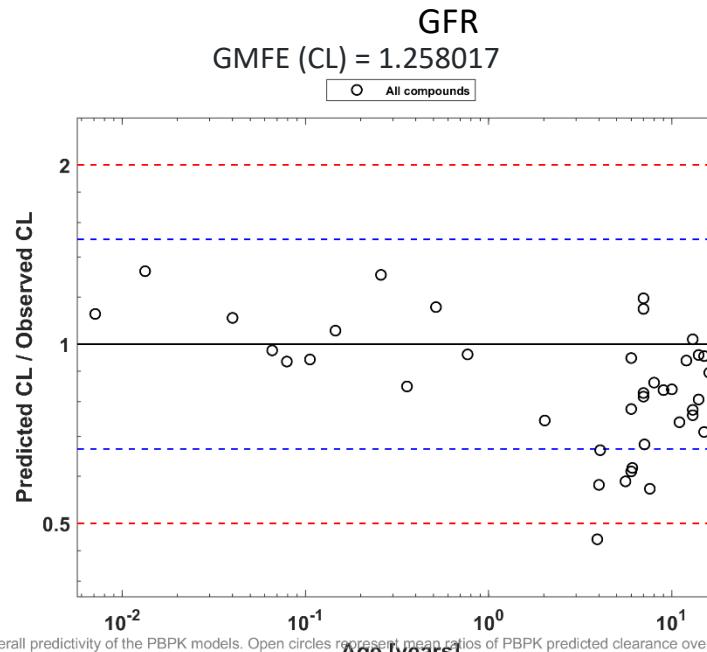
Ince et al. J Clin Pharmacol. 2019;59 Suppl 1:S95-S103.

# Pediatric Ontogeny Qualification

- There are novel guidelines published by the European Medicines Agency and the FDA on investigation of medicinal products in the pediatric population.
- Qualification of a PBPK platform and demonstration of confidence of an intended use for applications in regulatory submissions are specific requirements.
- By use of a developed and **verified (adult) PBPK** model for an in vivo probe substance, a pediatric PBPK model can be established for children by translating the adult physiology, clearance processes, protein binding, and the process-specific variabilities to children.
- For qualification purposes, during the translation of adult PBPK models to children the following **assumptions and considerations** are made:
  - When translating the adult model to children, it is assumed that the **contributing metabolism and excretion pathways are qualitatively the same in children as in adults**.
  - No further changes to drug or drug-biology interacting properties (e.g. lipophilicity parameter, intestinal permeability, solubility) are allowed during the simulations in children.
  - **Identical pathophysiology** in children as in adults

# Qualification reports of distribution, GFR and enzyme ontogenies

- Exemplary Qualification reports are published in GitHub
  - <https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports>



# Bridging from adults to children - Workflow

## Step 1:

**Development and verification** of a PBPK model for adults

## Step 2:

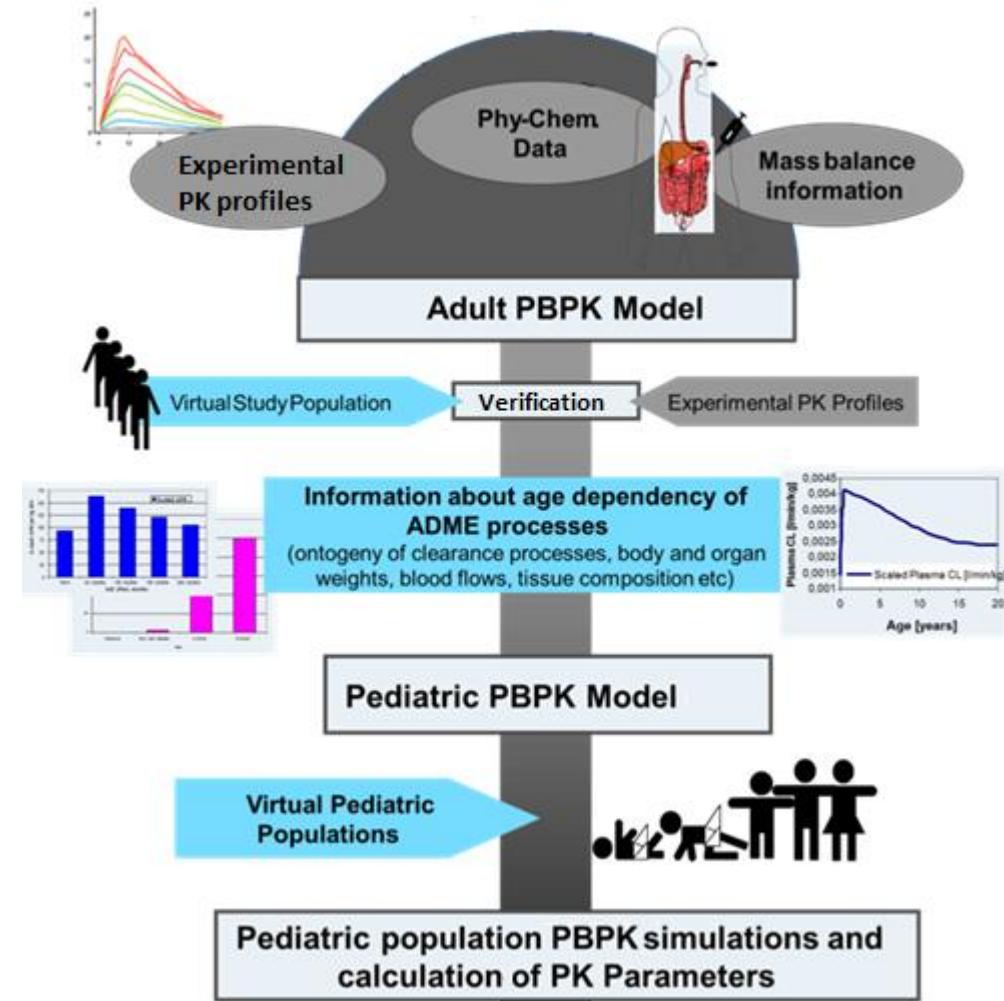
**Translation** of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

## Step 3:

**Prediction** of pharmacokinetics in children by means of simulations of virtual pediatric trials

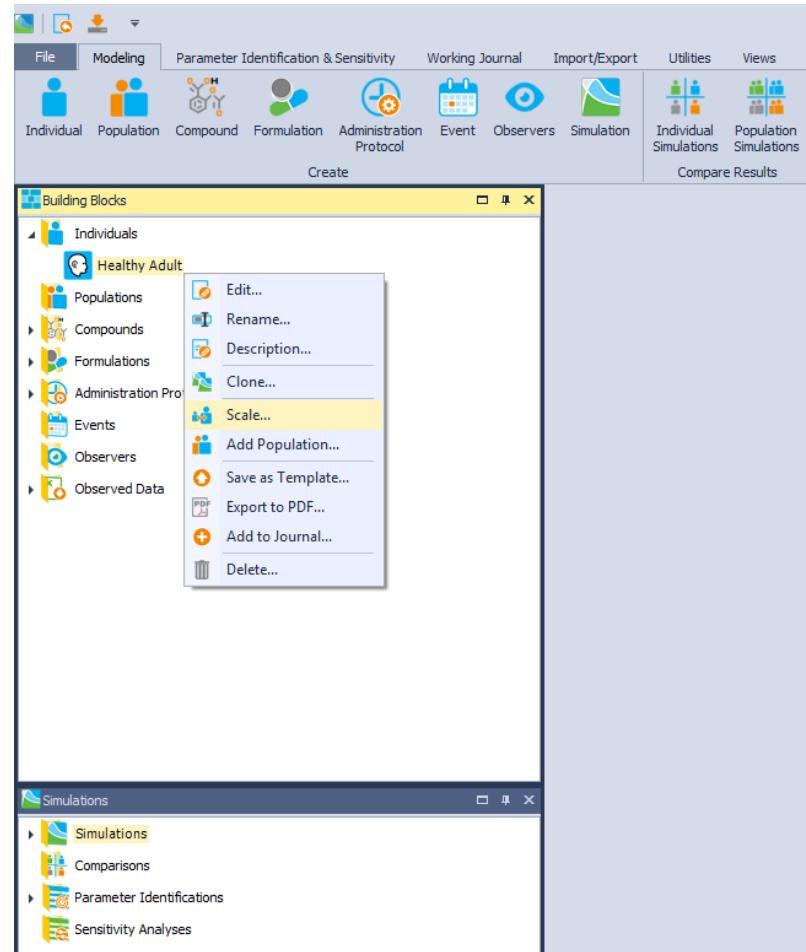
## Step 4:

**Support of clinical decision process** by evaluating adequate dosing, sampling or cohort size



# Workflow for Scaling Drug Pharmacokinetics Using PBPK

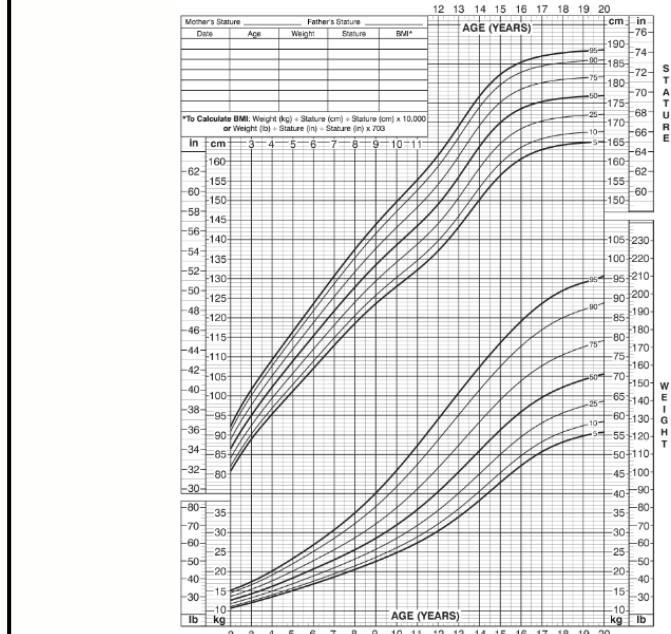
- One can scale an adult individual to
  - An individual child
  - A pediatric population



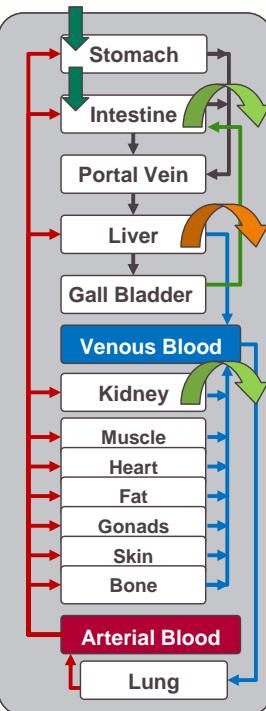
# Workflow for Scaling Drug Pharmacokinetics Using PBPK

- Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of physiological/anatomical information vs. age



[www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts)



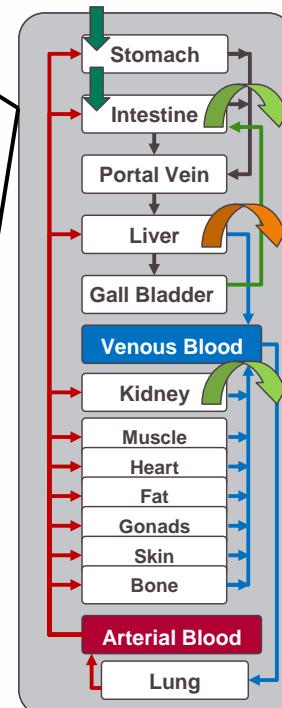
Willmann et al., Clin. Pharmacokinet. (2013)

# Workflow for Scaling Drug Pharmacokinetics Using PBPK

- Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of physiological/anatomical information vs. age

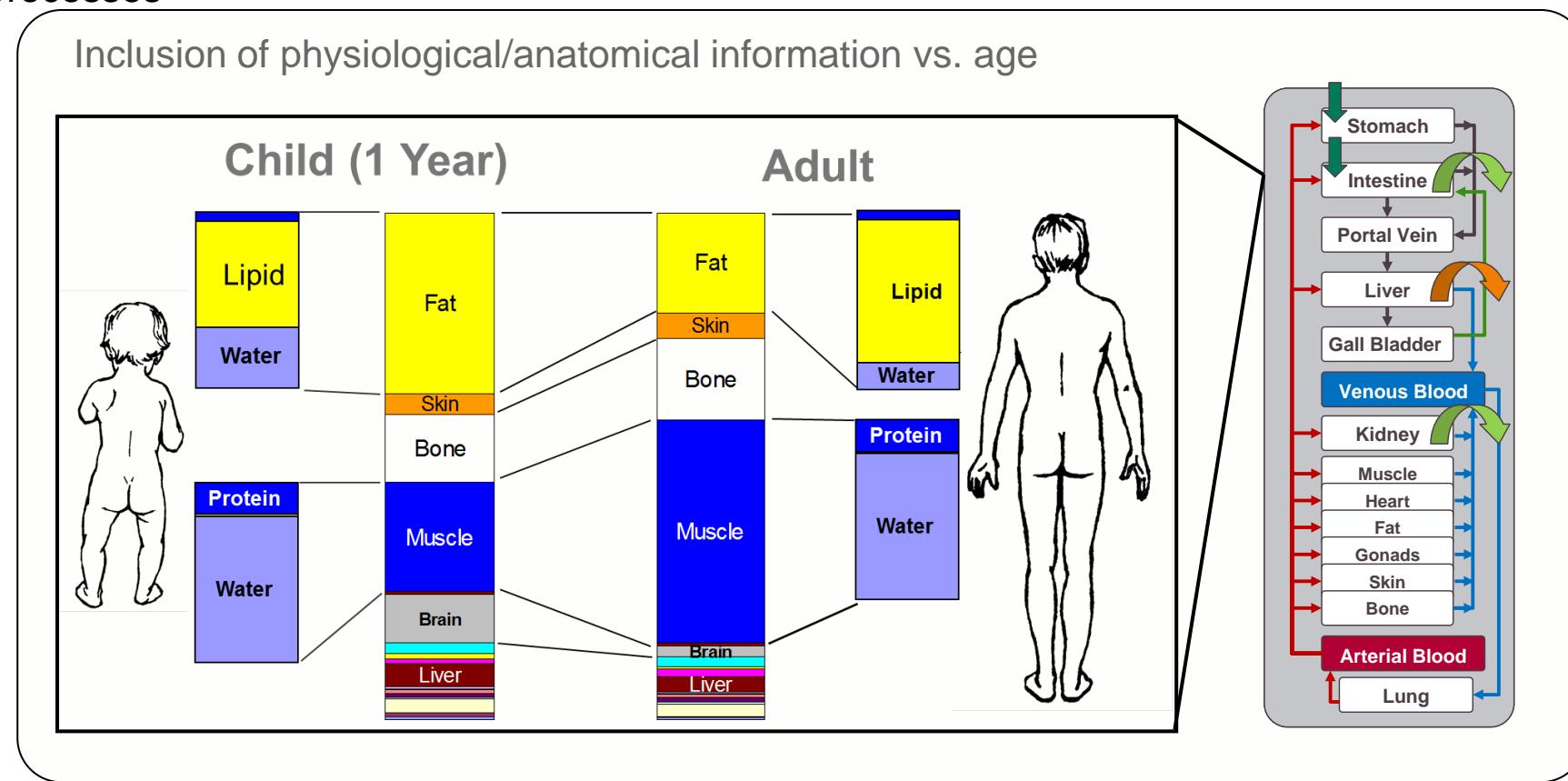
Parameter	Newborn	1y	5y	10y	15y	Adult (30y)
Organ blood flow (mL/min)						
adipose	30	12	171	250	315/484 <sup>a</sup>	325/502 <sup>a</sup>
brain	180	700	900	840/750 <sup>a</sup>	805/708 <sup>a</sup>	780/708 <sup>a</sup>
gonads	0.3	0.6	1.7/0.7 <sup>a</sup>	2.5/1.0 <sup>a</sup>	3.2/1.1 <sup>a</sup>	3.3/1.2 <sup>a</sup>
heart	24	48	136	200	252/285 <sup>a</sup>	260/295 <sup>a</sup>
kidneys	110	230	577	854	1335/950 <sup>a</sup>	1325/1120 <sup>a</sup>
large intestine	24	48	136	200	251/285 <sup>a</sup>	260/295 <sup>a</sup>
liver	39	78	221	325	409/370 <sup>a</sup>	423/383 <sup>a</sup>
muscle	31	72	212	429	941/646 <sup>a</sup>	1105/665 <sup>a</sup>
pancreas	6	12	34	50	63/57 <sup>a</sup>	65/59 <sup>a</sup>
skeleton	30	60	170	250	315/285 <sup>a</sup>	325/295 <sup>a</sup>
skin	30	60	170	250	315/285 <sup>a</sup>	325/295 <sup>a</sup>
small intestine	60	120	340	500	630/627 <sup>a</sup>	650/649 <sup>a</sup>
spleen	18	36	102	150	189/171 <sup>a</sup>	195/177 <sup>a</sup>
stomach	6.0	12	34	50	63/57 <sup>a</sup>	65/59 <sup>a</sup>
Portal blood flow (mL/min)	114	228	646	950/950 <sup>a</sup>	1197/1197 <sup>a</sup>	1235/1239 <sup>a</sup>
Q <sub>H</sub> (mL/min)	153	306	867	1275/1273 <sup>a</sup>	1600/1566 <sup>a</sup>	1660/1620 <sup>a</sup>
Bodyweight (kg)	3.5	10	19	32	56/53 <sup>a</sup>	73/60 <sup>a</sup>
Height (cm)	51	76	109	138	167/161 <sup>a</sup>	176/163 <sup>a</sup>
<sup>a</sup> Male/female.						



Willmann et al., Clin. Pharmacokinet. (2013)

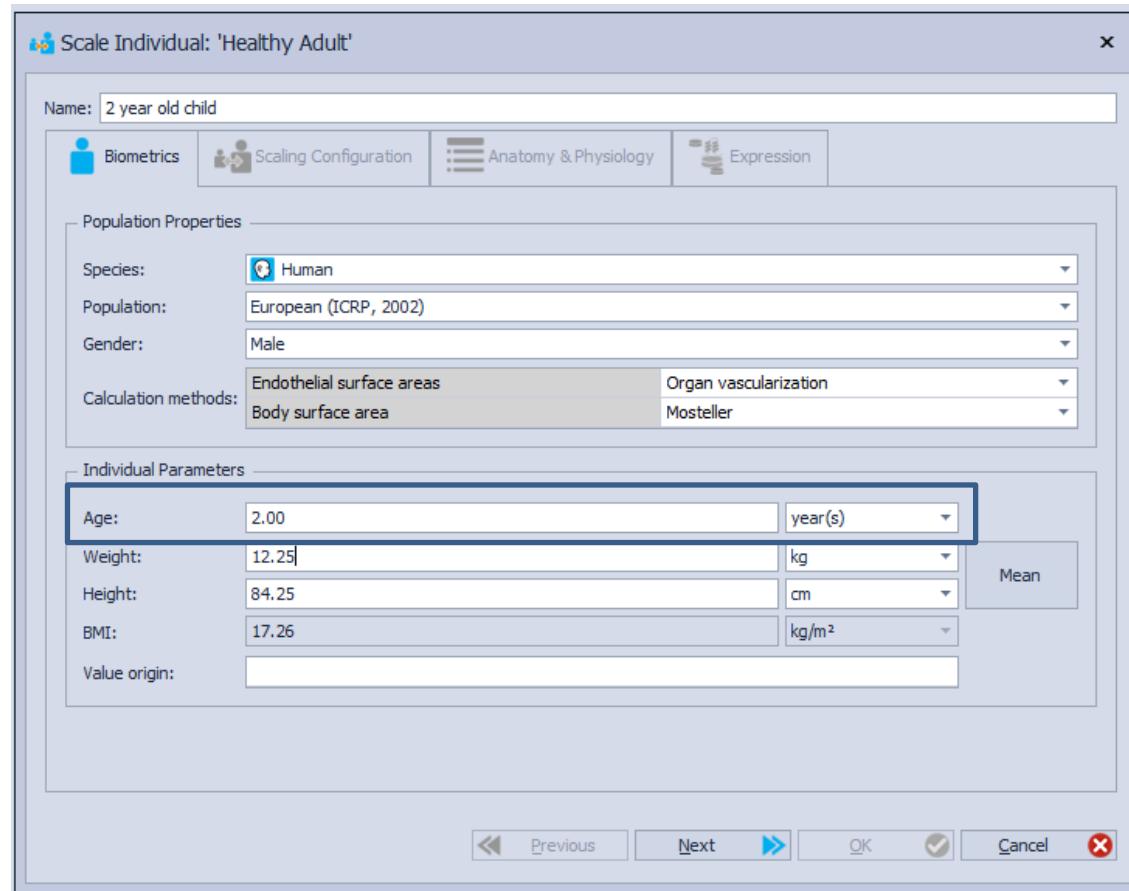
# Workflow for Scaling Drug Pharmacokinetics Using PBPK

- Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes



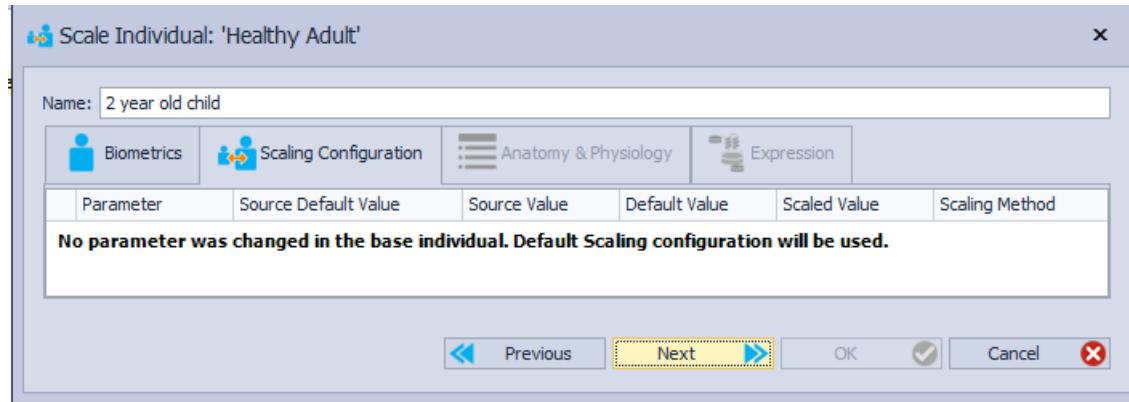
Willmann et al., Clin. Pharmacokinet. (2013)

# Define pediatric demographics

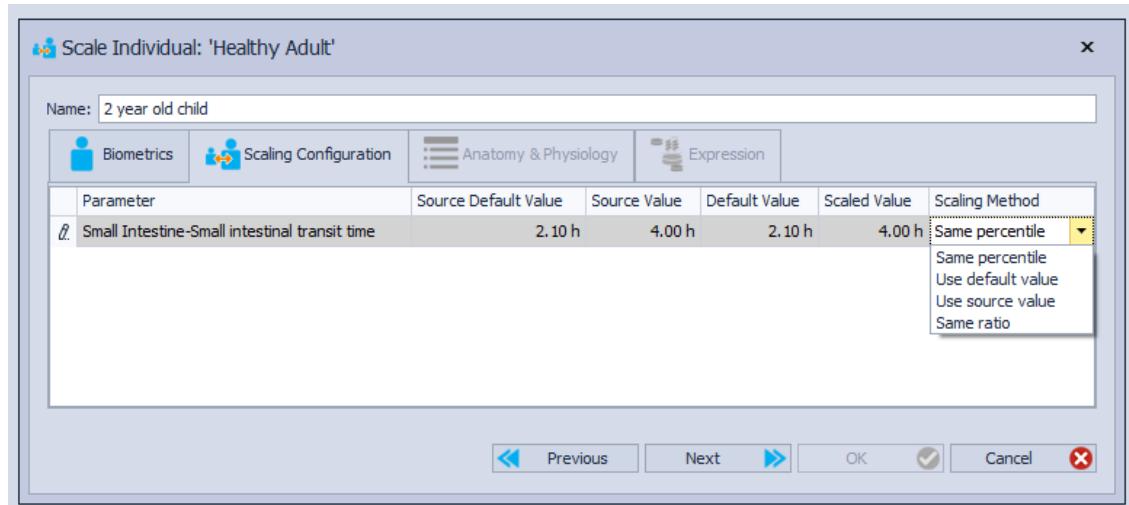


- for a typical individual child to be scaled to, at least the Age must be imputed
- From this, a typical weight and height will be assigned to that age, and a BMI will be calculated

# Scaling configuration



- In case of no deviation from the ‘standard’ parameter values in adults, this tab will be empty



- In case a manual adjustment in one of the PK parameters was set in the adult
- One has to indicate how to scale this parameter to the child

# Anatomy & Physiology

Scale Individual: 'Healthy Adult'

Name: 2 year old child

**Scaling Configuration**

**Anatomy & Physiology**

**Expression**

**Filter**

- Favorites
- User Defined
- Characteristics of individual
- Anatomy**
  - GIT - Dimensions
  - Organ volumes**
    - Mucosa (total)
    - Vascular endothelium
    - Volume gut wall
  - Surface area
- Physiology
- All

**Category**

Organ	Value	Percentile	Value Origin	Favorites
Venous Blood	0.14l	50%	Publication-ICRP,...	<input type="checkbox"/>
Arterial Blood	0.06l	50%	Publication-ICRP,...	<input type="checkbox"/>
Bone	1.74l	50%	Publication-ICRP,...	<input type="checkbox"/>
Brain	1.08l	51%	Publication-ICRP,...	<input type="checkbox"/>
Fat	4.05l	51%	Publication-ICRP,...	<input type="checkbox"/>
Gonads	1.86E-3l	50%	Publication-ICRP,...	<input type="checkbox"/>
Heart	0.08l	50%	Publication-ICRP,...	<input type="checkbox"/>
Kidney	0.12l	50%	Publication-ICRP,...	<input type="checkbox"/>
Large Intestine	0.08l	50%	Publication-ICRP,...	<input type="checkbox"/>
Liver	0.54l	51%	Publication-ICRP,...	<input type="checkbox"/>
Liver Periporal	0.54l		Publication-ICRP,...	<input type="checkbox"/>
Liver Pericentral	0l		Publication-ICRP,...	<input type="checkbox"/>
Lung	0.23l	40%	Publication-ICRP,...	<input type="checkbox"/>
Muscle	3.27l	49%	Publication-ICRP,...	<input type="checkbox"/>
Pancreas	0.03l	50%	Publication-ICRP,...	<input type="checkbox"/>
Portal Vein	0.15l	50%	Publication-ICRP,...	<input type="checkbox"/>
Saliva	1.01E-3l		Internet-Willi Ca...	<input type="checkbox"/>

Scale 1.00

Previous  OK  Cancel

- In the Anatomy & Physiology tab, some parameters can be further adjusted from the scaled typical vale, e.g. organ volumes
  - Only in case you have good reason to do so!
  - E.g. due to known pathophysiology reasons

# Expression configuration

Screenshot of the 'Scale Individual: 'Healthy Adult'' dialog box, specifically the 'Expression' tab for CYP1A2.

**Name:** 2 year old child

**Metabolizing Enzymes -> CYP1A2**

**Properties**

Name	Value	Value Origin
Reference concentration	1.80 µmol/l	
t <sub>1/2</sub> (liver)	39.00 h	
t <sub>1/2</sub> (intestine)	23.00 h	

Ontogeny/variability like: CYP1A2

**Localization**

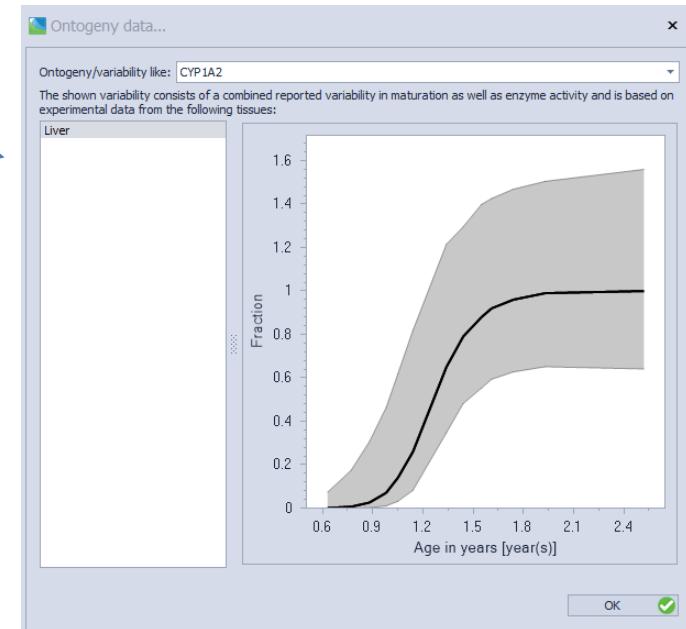
Localization in tissue: Intracellular

Localization in vasc. endothelium: Endosomal

	Relative Expression	Normalized Expression
<b>Vascular system</b>		
Blood Cells	0	0%
Plasma	0	0%
Vascular Endothelium	0	0%
<b>Organs, tissues &amp; matrices</b>		
Bone	0.20	20%
Brain	0.11	11%
Fat	0	0%

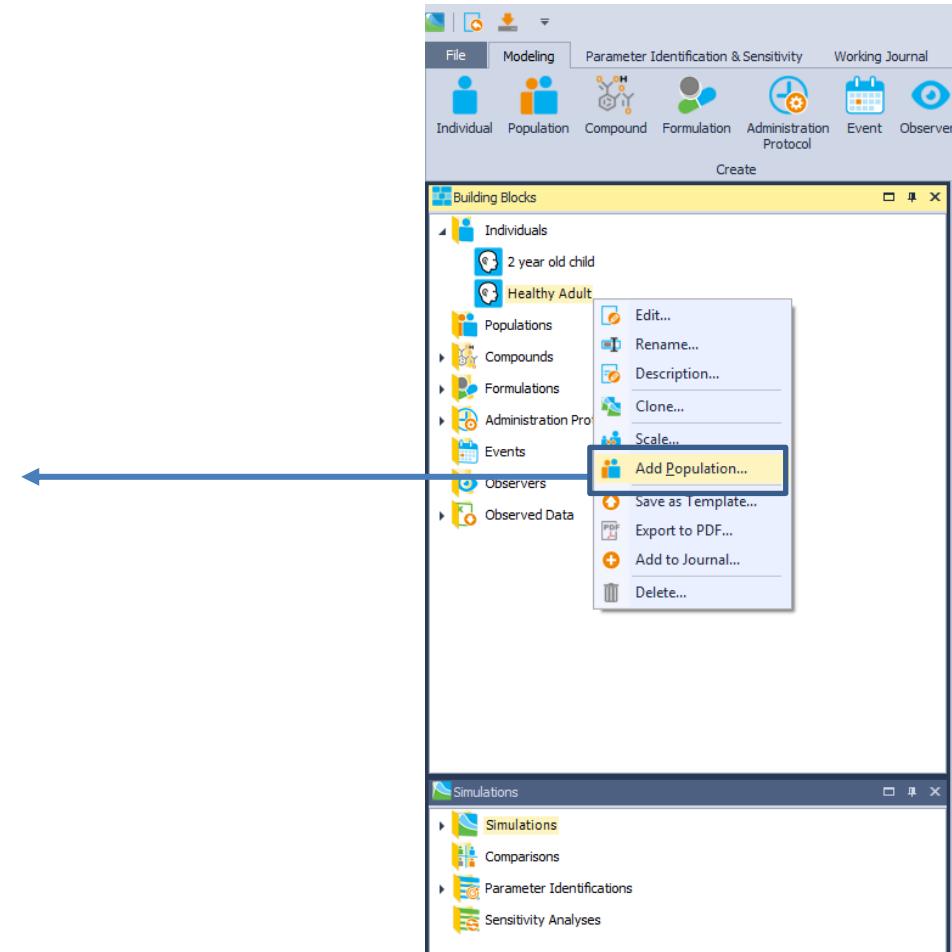
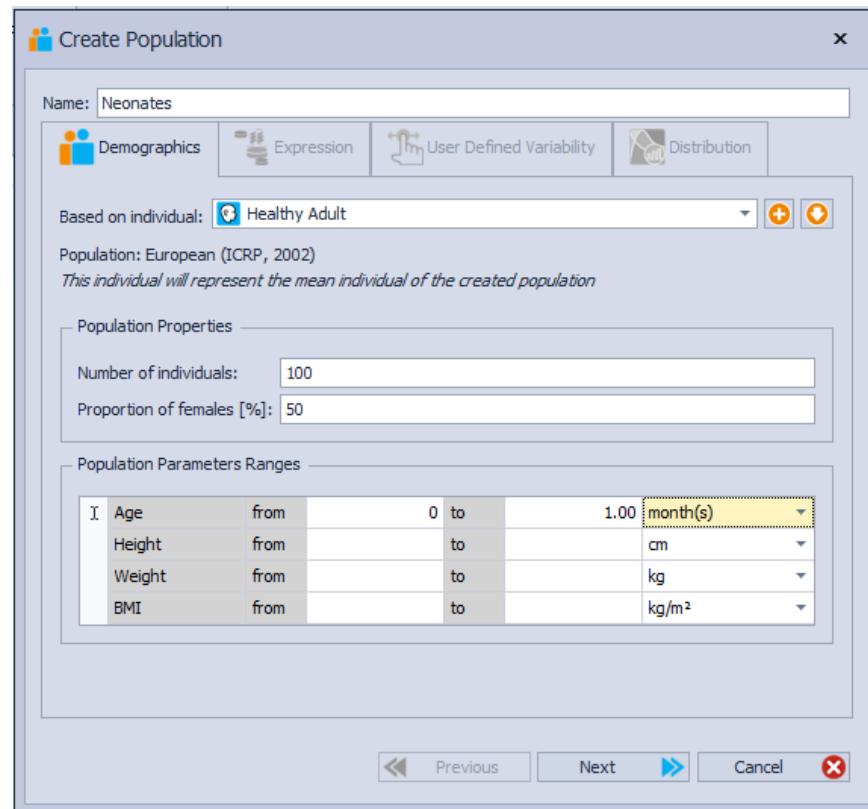
Previous Next OK Cancel

- In the expression tab, in case of active processes are involved, the properties can be adjusted
  - However generally these parameters are assumed not to be changed in children during scaling, other than the built-in ontogeny factor shown below which automatically changes

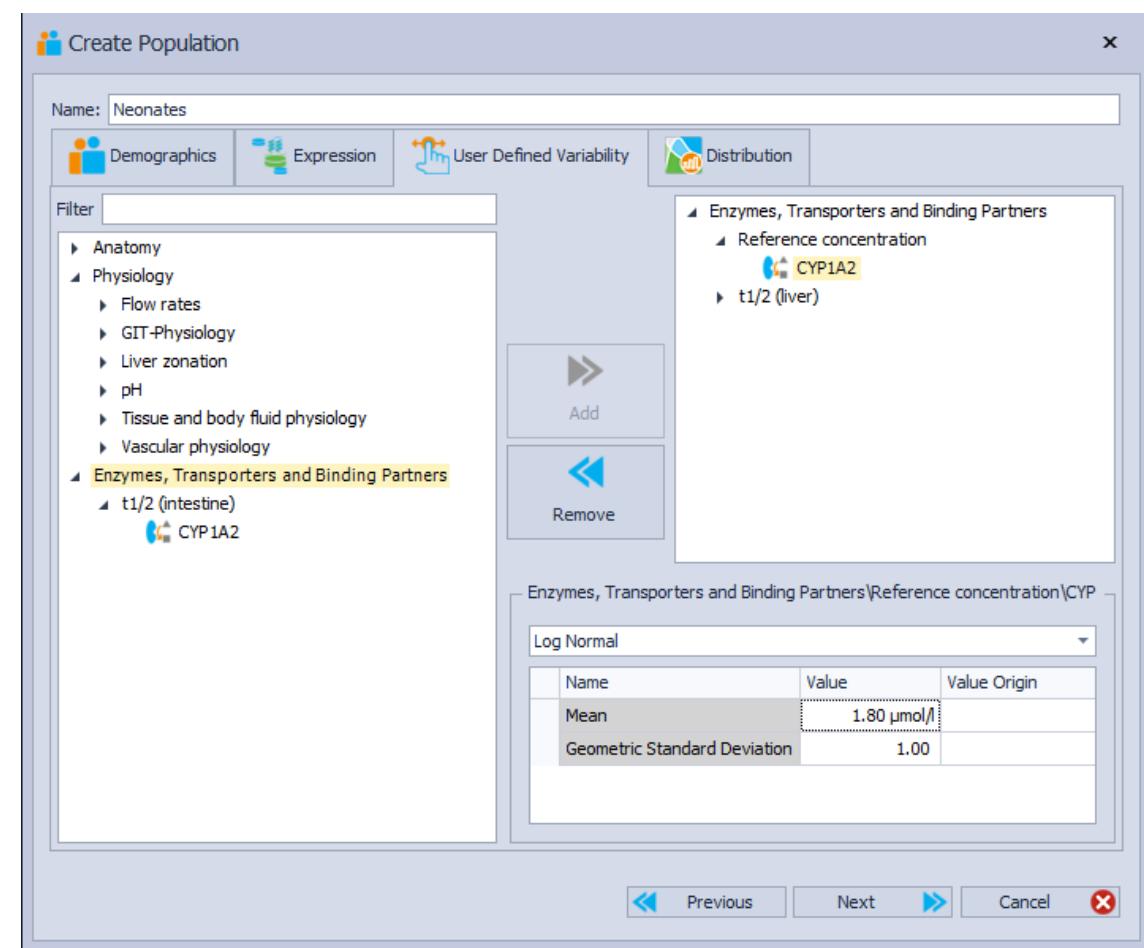
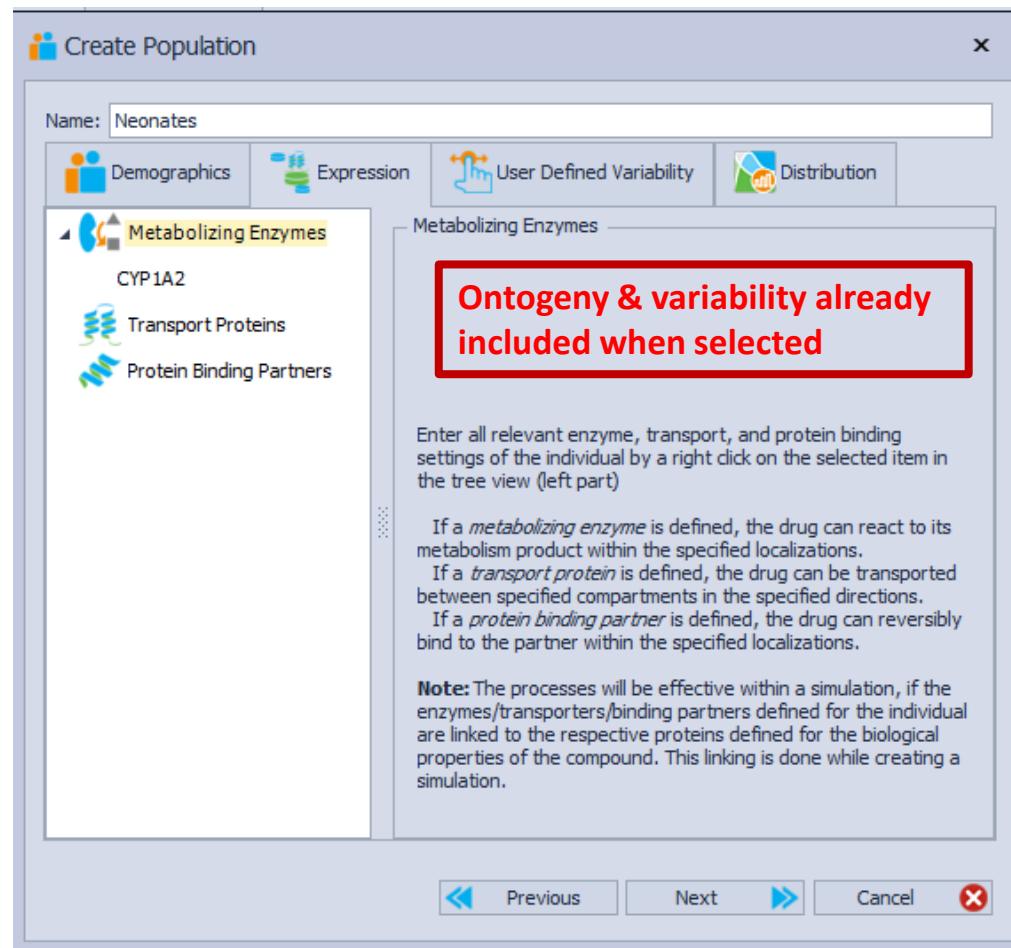


# Scaling to a pediatric population

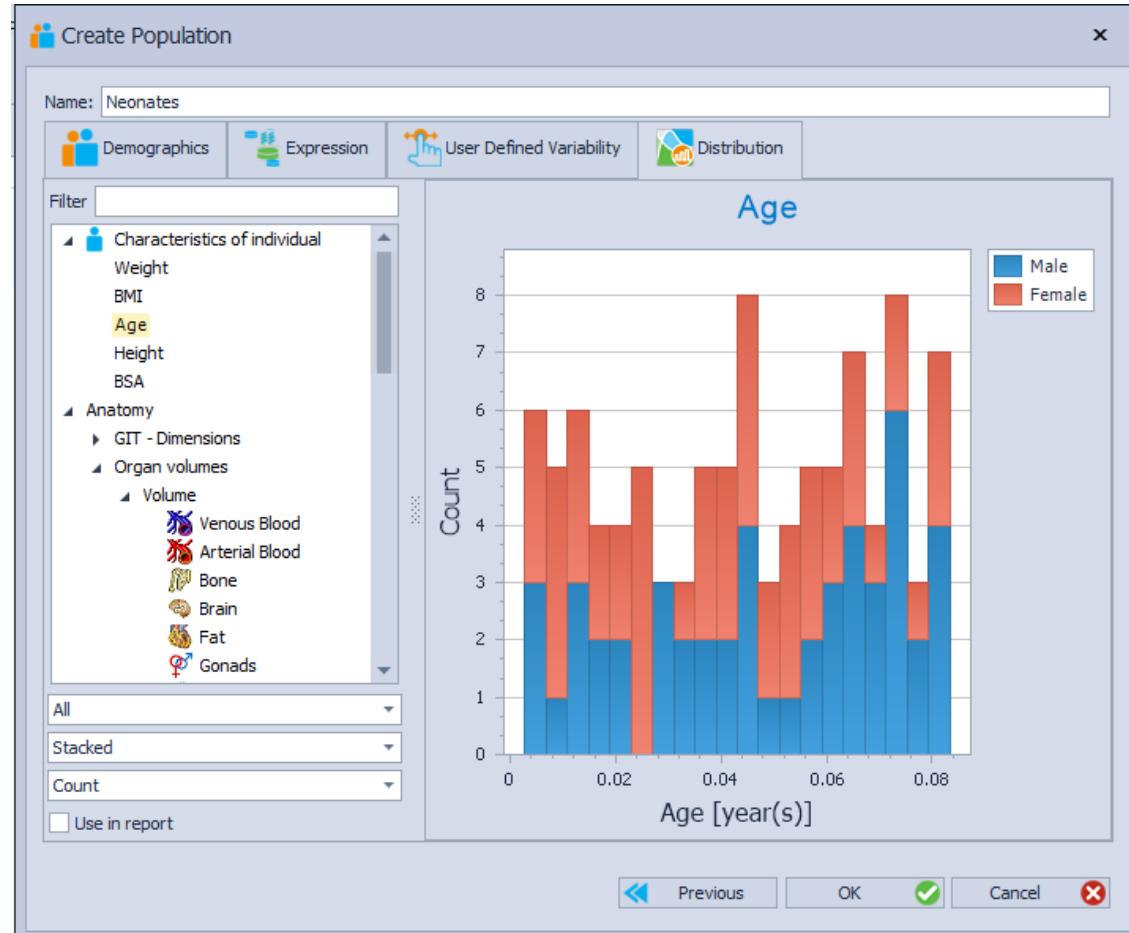
- One can scale an adult individual to
  - A pediatric population



# Define expression and additional variability



# Overview of parameter distribution

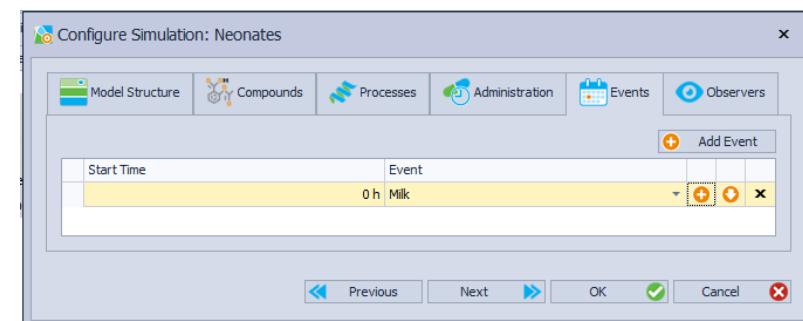
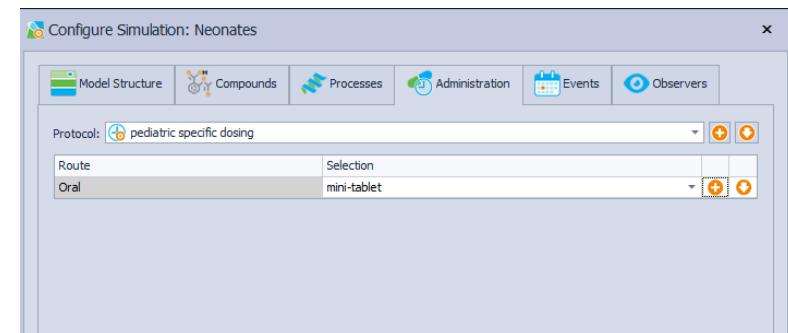


- In the distribution tab, a distribution of the variable parameters are shown for information
- As soon as the population is created the next step would be to create a simulation from the pediatric individual or population

# Configure and run simulation

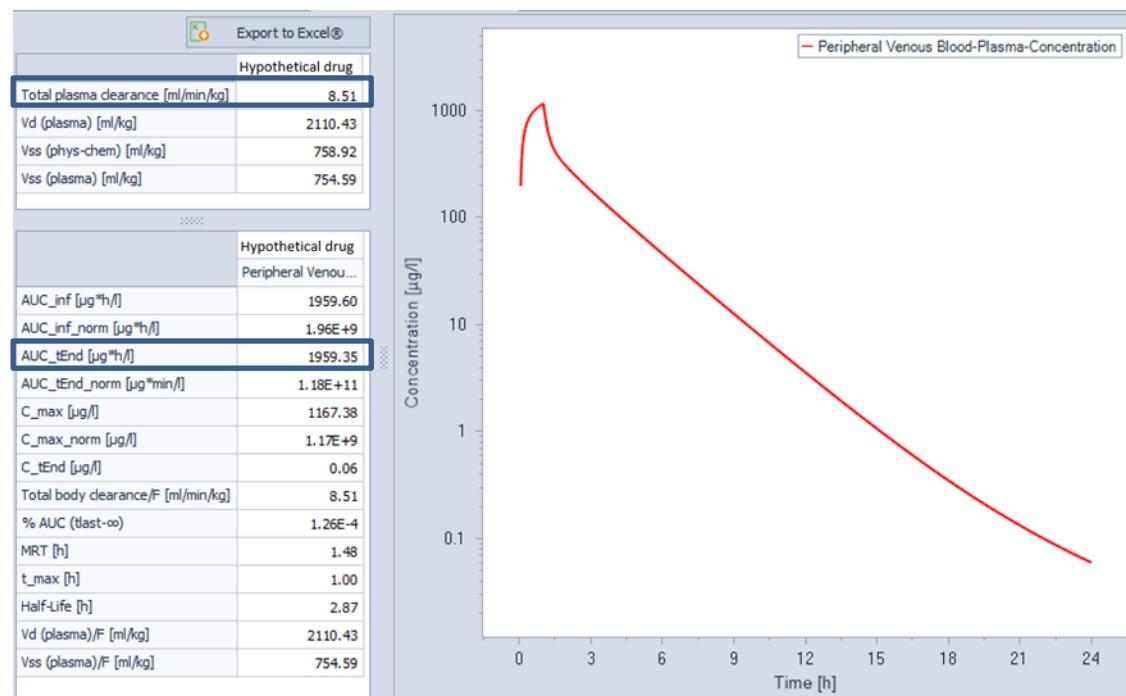


- The only difference to an adult individual/population simulation is to select the pediatric individual/ population of interest, and possibly the formulation, dose, food-intake in their respective tabs.

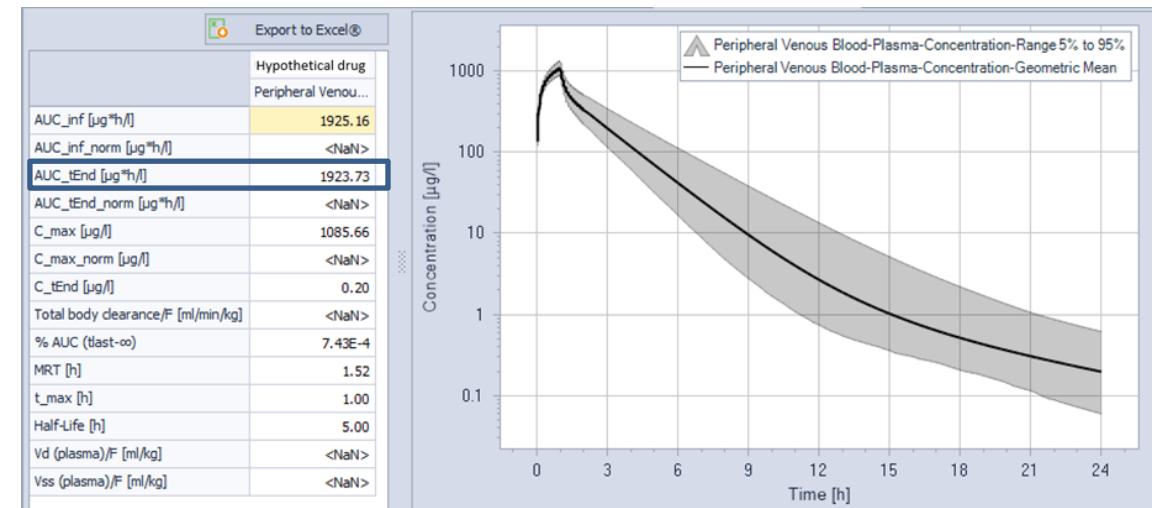


# Simulation results

Individual Simulation



Population Simulation



- The derived PK-parameters from the simulations can be then used to support clinical decision process by evaluating adequate dosing, sampling or cohort size

# Bridging from adults to children - Workflow

## **Step 1:**

**Development and verification**  
of a PBPK model for adults

## **Step 2:**

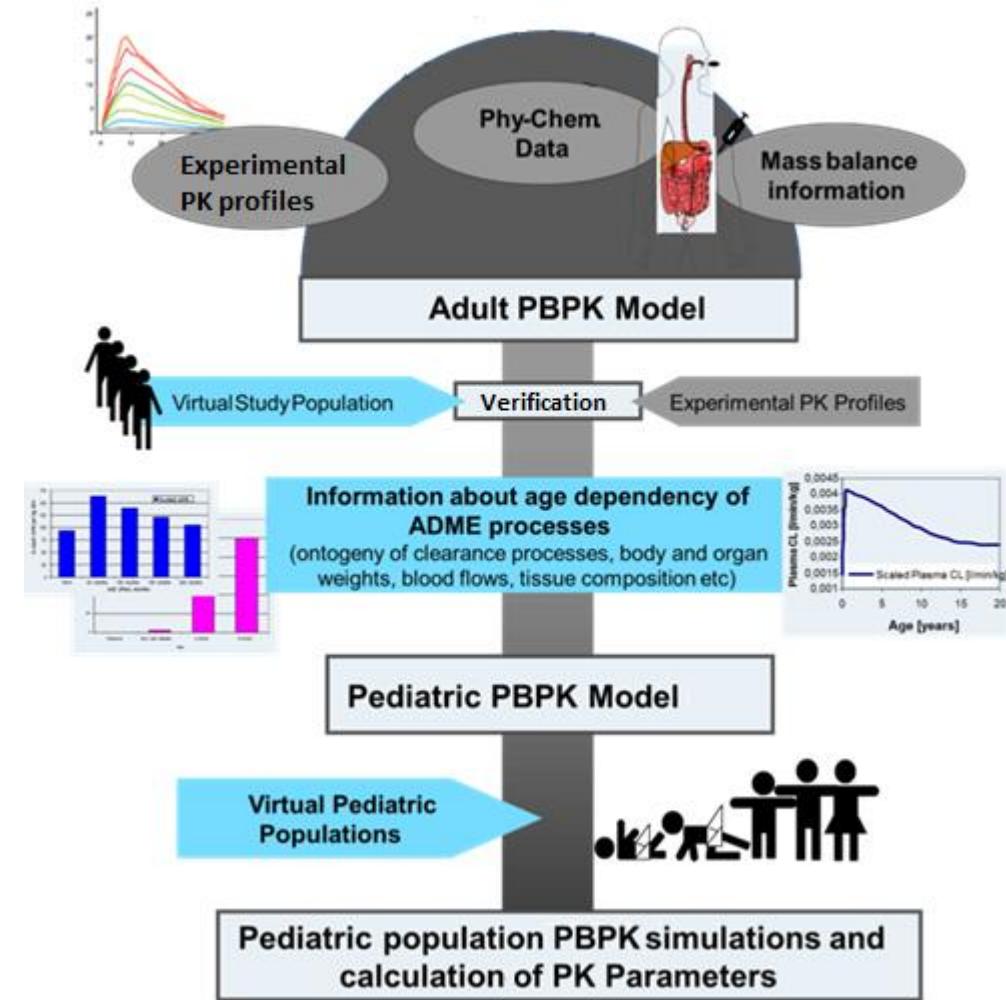
**Translation** of the adult PBPK model  
to children using prior physiological information  
about growth and maturation of relevant  
processes

## **Step 3:**

**Prediction** of pharmacokinetics  
in children by means of simulations of virtual  
pediatric trials

## **Step 4:**

**Support of clinical decision process** by evaluating  
adequate dosing, sampling or cohort size



# Picking the Right Dose

- Simulation of Rivaroxaban pharmacokinetics in pediatric populations for treatment of venous thromboembolism (VTE)



# Pediatric dosing schemes in children supported by PBPK predictions

- Overview of Bayer small molecule compounds applied in children since 2005

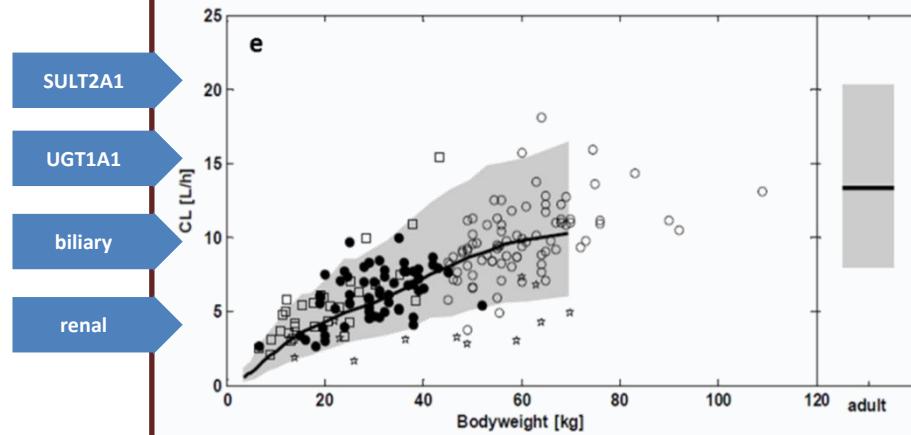
Market Name	Age range (years)	Involved processes in PBPK model
<b>Amikacin</b>	<b>0.01 – 16</b>	<b>GFR</b>
<b>Ciprofloxacin</b>	<b>0.2 – 6.6</b>	<b>CYP1A2, TS, GFR, Bil.CL</b>
<b>Copanlisib</b>	<b>13 – 17</b>	<b>CYP3A4, PgP, PIK3a</b>
<b>Gadovist</b>	<b>0.2 – 18</b>	<b>GFR</b>
<b>Levonorgestrel</b>	<b>12 – 18</b>	<b>Hepatic CL</b>
<b>Magnevist</b>	<b>0.2 – 2</b>	<b>GFR</b>
<b>Moxifloxacin</b>	<b>0 – 18</b>	<b>UGT1A1, SULT2A1, Bil.CL, TS/GFR</b>
<b>Regorafenib</b>	<b>2 – 17</b>	<b>CYP3A4, UGT1A9, Bil.CL</b>
<b>Riociguat</b>	<b>6 – 18</b>	<b>CYP1A1, CYP3A4, CYP3A5, CYP2C8, CYP2J2, UGT1A2, UGT1A9, Bil.CL (Pgp, BCRP), TS/GFR</b>
<b>Rivaroxaban</b>	<b>0 – 18</b>	<b>CYP3A4, Plasma Hydrolysis, GFR, TS, CYP2J2</b>
<b>Sorafenib</b>	<b>1 – 19</b>	<b>CYP3A4, UGT1A9, Reduction, Unspecific CL</b>

\* TS : tubular secretion, Bil.CL: biliary clearance, PIK3a: phosphatidylinositol 3-kinase alpha

Ince et al. Accepted for publication 2021 @ J Clin Pharmacol.

# Prospective evaluation of PBPK predictions with data observed during clinical studies in children confirms predictive power

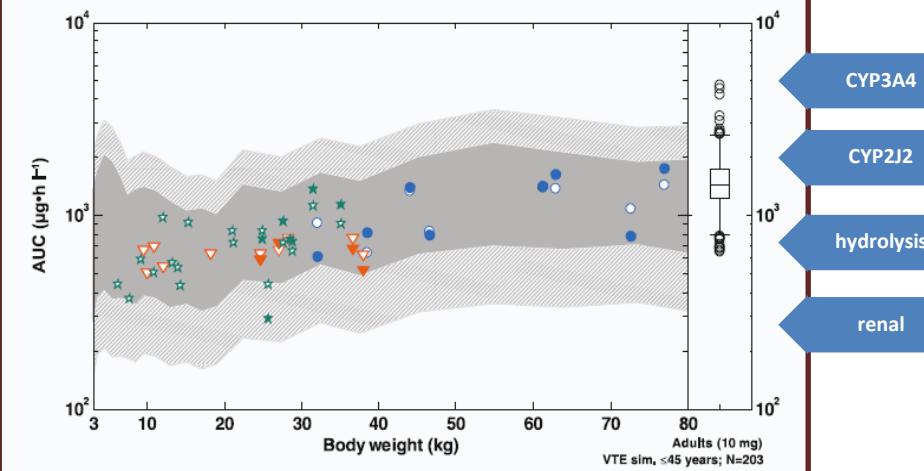
*Example: Moxifloxacin*



black line: PBPK prediction for children (median)  
gray shaded area: PBPK prediction for children (90% interval)  
symbols: individual data derived from clinical observations using population PK modelling in pediatric phase 1 and 3 trials following single or multiple oral or intravenous doses

Willmann et al., *CPT Pharmacometrics Syst Pharmacol.* (2019)

*Example: Rivaroxaban*



dark gray area: PBPK prediction for children (90% interval)  
light gray area: extended PBPK prediction range (0.5 x 5<sup>th</sup> to 1.5 x 95<sup>th</sup> percentile)  
symbols: individual data derived from clinical observations following single administration of 10 mg-equivalent dose

Willmann et al., *Thrombosis Journal* (2018)

# Evaluation of 10 Bayer Compounds applied in Children

- Evaluated pediatric PBPK models for 10 Bayer compounds
  - Via Ratio-calculation PBPK vs reported PK (popPK and NCA of clinical data)

Ratio of Predicted PBPK vs PopPK and NCA of clinical data-based PK-Parameters	
Evaluation of predictive performance	AUC <sub>24,ss</sub> C <sub>trough</sub> C <sub>365days</sub> Clearance
Predefined age groups	0-<2 years 2-<6 years 6-<12 years 12-<18 years
PBPK simulation software	Open Systems Pharmacology (OSP) Suite (PK-Sim / MoBi) * (or formerly BTS Computational Systems Biology Suite)
Calculation & Illustration software	Rstudio Version 1.2.5033

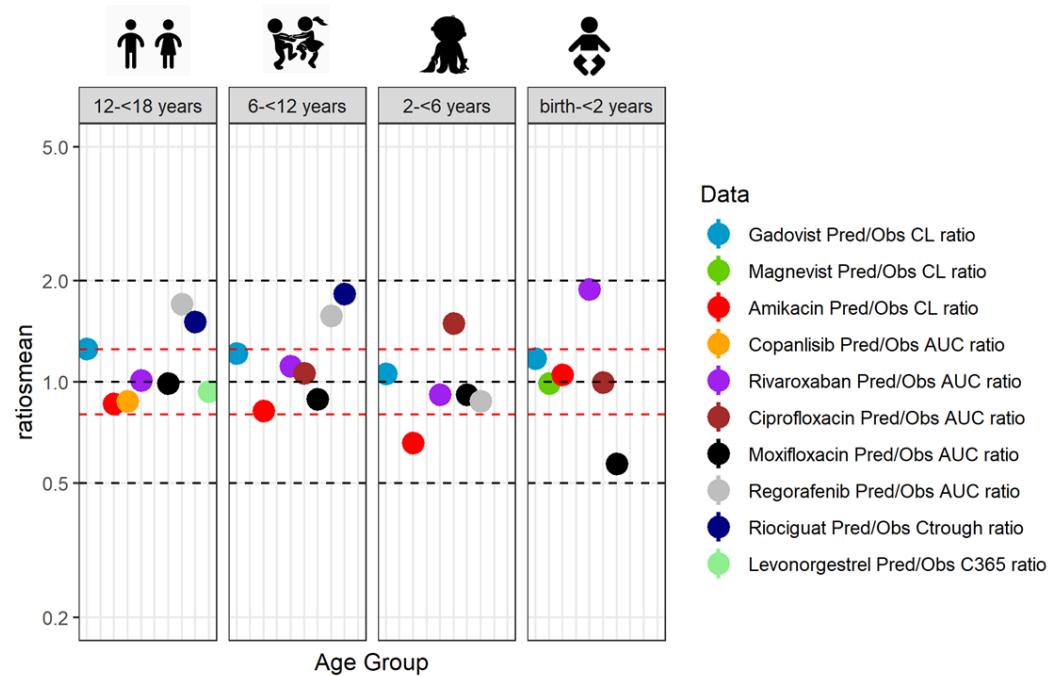
Ince et al. Accepted for publication 2021 @ J Clin Pharmacol.

# Confirmation of predictive power of PBPK in real life

- Predicted versus observed

- For all pediatric age groups

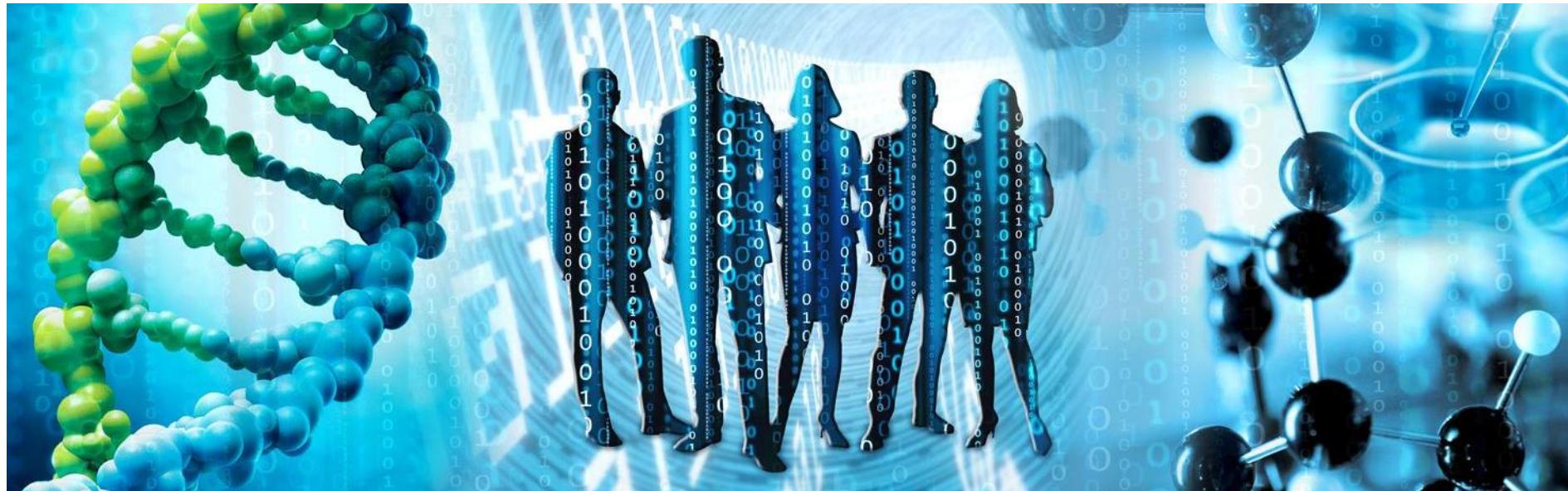
- 100% of observed data within 2-fold range of prediction
- 67% within BE interval



Ince et al. Accepted for publication 2021 @ J Clin Pharmacol.

# Questions

Open-Systems-Pharmacology.org



<https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports>

## Hands-on:

### Derive optimal dose for children

---

- Hands-on exercises
  - Intro part 1 (*2 min*)
  - Establish a pediatric PBPK model (*20 min*)
  - Intro part 2 (*2 min*)
  - Perform Population Simulation in Children (*20 min*)

# Part 1 - Establish a pediatric PBPK model

- Scale an adult model to a female child aged 1 year old and simulate the pk of “Drug” after 100mg IV administration
  - *Adult PBPK model is already established ([Session3\\_HandsOn\\_1.pksim5](#))*
  - *Take into account the ontogeny of enzyme\_liv (use file ‘[Ontogeny for enzyme\\_liver.xlsx](#)’)*

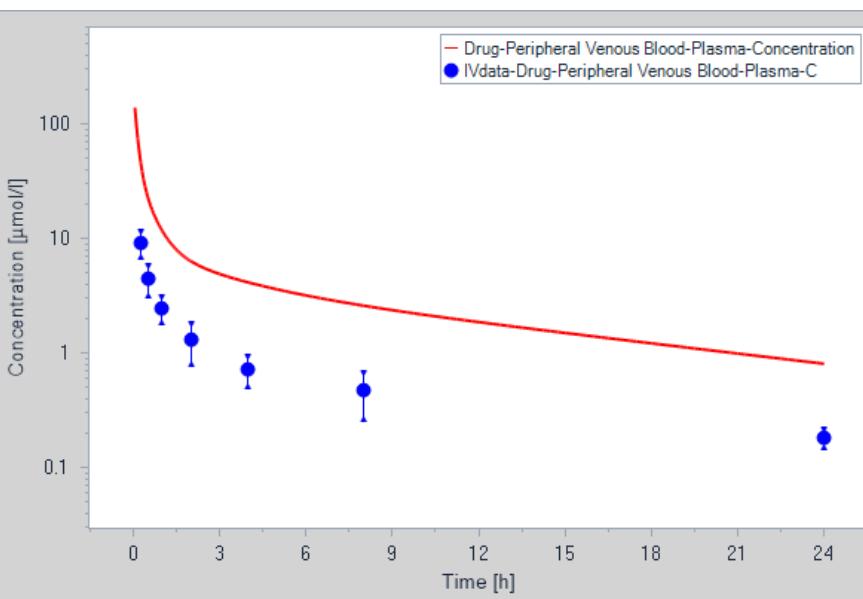
Compare Exposure after 24h (AUC\_tEnd) with the adult

- *Use the option ‘[Compare Results](#)’ in ‘Run & Analyze’ to overlay the adult and pediatric simulation*

- Simulate a mg dose for a 1 year old child equivalent to an adult of 73kg receiving 100mg IV
  - *Part 1 exercise PBPK model can be used ([Session3\\_HandsOn\\_2.pksim5](#))*
  - *Calculate the difference in exposure and simulate the fold difference in dose in the 1 year old child*

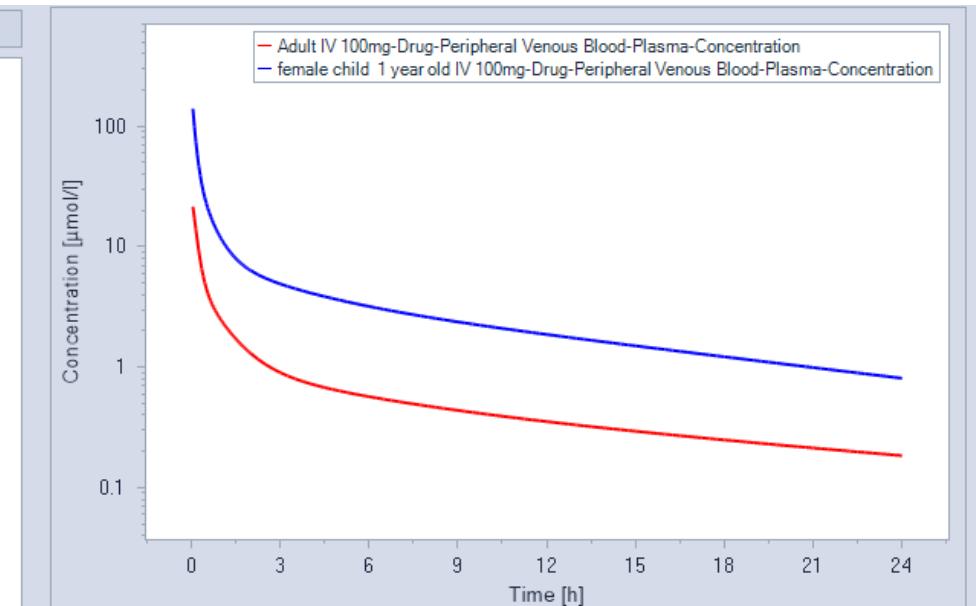
Compare again the Exposure after after 24h (AUC\_tEnd) with the adult

# Simulating 100mg IV in 1 year old child versus adult

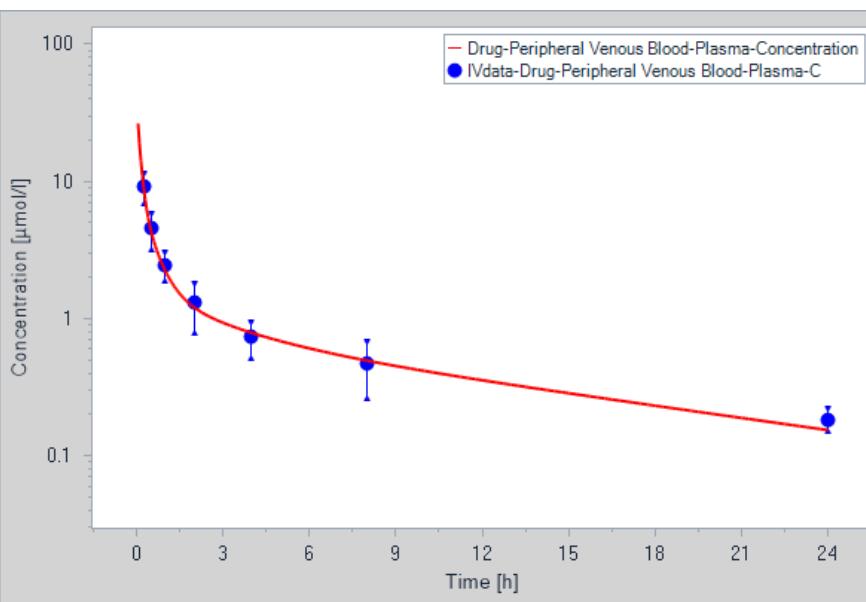


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	Drug	
AUC_inf [ $\mu\text{mol}^*\text{min}/\text{l}$ ]	1271.38	6188.45
AUC_inf_norm [ $\mu\text{g}^*\text{min}/\text{l}$ ]	3.71E+11	2.48E+11
<b>AUC_tEnd [<math>\mu\text{mol}^*\text{min}/\text{l}</math>]</b>	<b>1040.18</b>	<b>5473.17</b>
AUC_tEnd_norm [ $\mu\text{g}^*\text{min}/\text{l}$ ]	3.04E+11	2.19E+11
C_max [ $\mu\text{mol/l}$ ]	21.49	139.67
C_max_norm [ $\text{mg/l}$ ]	6.27E+06	5.59E+06
C_tEnd [ $\mu\text{mol/l}$ ]	0.18	0.81
Total body clearance/F [ $\text{ml}/\text{min}/\text{kg}$ ]	2.69	4.04
% AUC ( $t_{last}-\infty$ )	0.18	0.12
MRT [h]	12.56	9.08
t_max [h]	0.05	0.05
Half-Life [h]	14.45	10.19
Vd (plasma)/F [ $\text{ml}/\text{kg}$ ]	3368.46	3563.01
Vss (plasma)/F [ $\text{ml}/\text{kg}$ ]	2029.88	2201.98

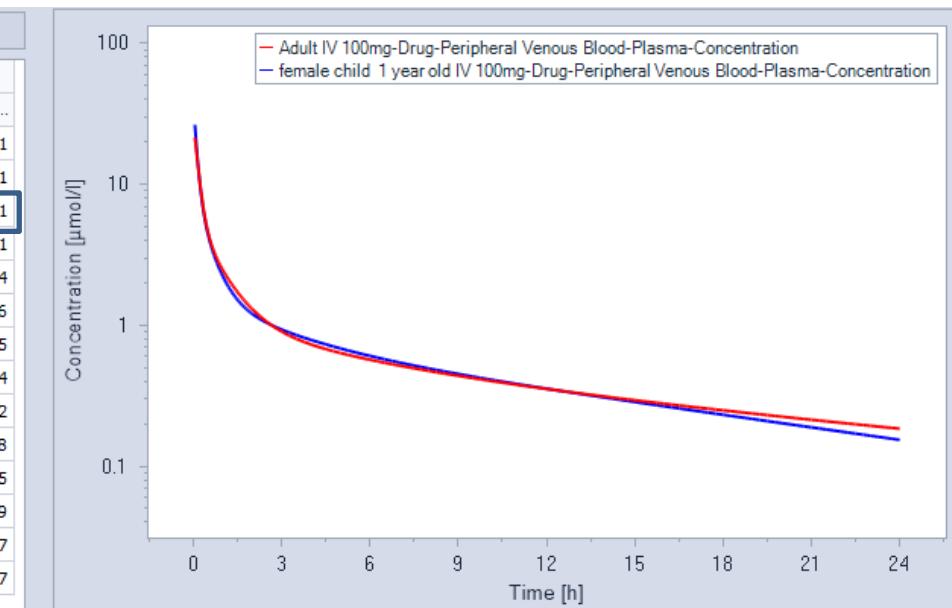


# Simulating scaled dose in 1 year old child versus adult



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Drug	
Adult IV 100mg...	female child 1 ye...
AUC_inf [ $\mu\text{mol}^*\text{min}/\text{l}$ ]	1271.38
AUC_inf_norm [ $\mu\text{g}^*\text{min}/\text{l}$ ]	3.71E+11
<b>AUC_tEnd [<math>\mu\text{mol}^*\text{min}/\text{l}</math>]</b>	<b>1040.18</b>
AUC_tEnd_norm [ $\mu\text{g}^*\text{min}/\text{l}$ ]	3.04E+11
C_max [ $\mu\text{mol/l}$ ]	21.49
C_max_norm [ $\text{mg/l}$ ]	6.27E+06
C_tEnd [ $\mu\text{mol/l}$ ]	0.18
Total body clearance/F [ $\text{ml/min/kg}$ ]	2.69
% AUC (tlast- $\infty$ )	0.18
MRT [h]	12.56
t_max [h]	0.05
Half-Life [h]	14.45
Vd (plasma)/F [ $\text{ml/kg}$ ]	3368.46
Vss (plasma)/F [ $\text{ml/kg}$ ]	2029.88
	2201.97



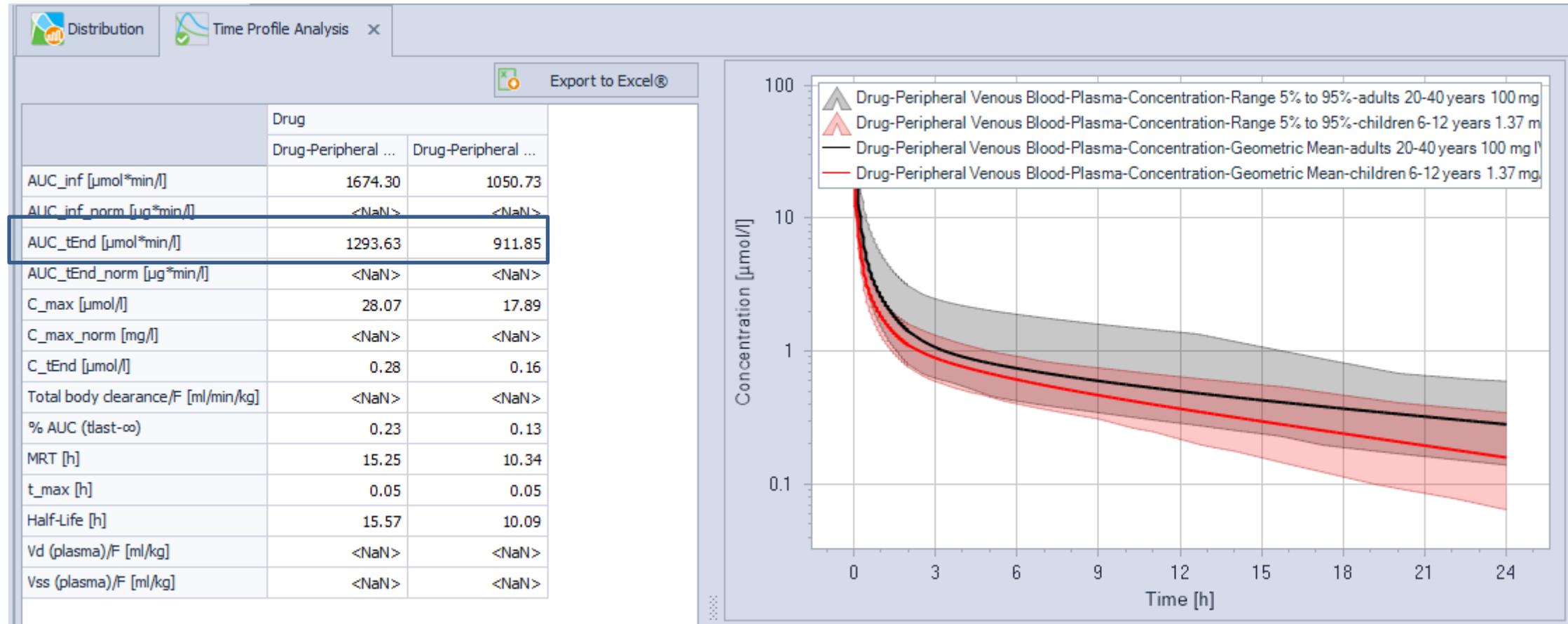
## Part 2 – Perform Population Simulation in Children

- Create a pediatric population between 6-12 years old and simulate the geo.mean time profile for “Drug” including 90% confidence intervals
  - *Part 1 exercise PBPK model can be used (Session3\_HandsOn\_3.pksim5)*
  - *Simulate 100 children between 6-12 years old*
  - *Use the created child building block including ontogeny*
  - *Apply 1.37 mg/kg (100mg /73kg adult) IV*

Compare Exposure of the pediatric population after 24h (AUC\_tEnd) with a simulated adult population

- *create first 100 adults between 20-40 years old and replace the individual adult in the simulation*
- **Optional:** investigate potential impact of differences in oral formulations and food (use Session3\_HandsOn\_4.pksim5)

# Comparison Exposure children versus adults using same mg/kg dose



# Potential impact of differences in oral formulations and food

