esqlabs
we empower life sciences

PQRI Workshop

Model-Informed Drug Development (MIDD) Approaches in Pediatric Formulation Development:

In-Silico Assessment

Day 2 – Thursday, February 29, 2024, Stephan Schaller

Agenda

01 **ESQlabs Intro**
Who we are, what we offer

02 **OSP Software**
Open-source PBPK and QSP

03 **OSP: Oral PK**

04 **OSP: Pediatrics**

05 **Examples**

06 **Summary & Outlook**

01

ESQlabs Intro

Who we are

Who We Are

We Conduct Model-based Assessment in the Life Sciences (Health and Chemical Industry)

"Competent service partner to support our customers decision making process along the entire life cycle of pharmaceutical & chemical products (from R&D to application)"


Mark Davies: BD Lead


Stephan Schaller: CEO, Lead Scientist


René Meyer: Finance Lead


Laura Kata: Operations Manager

Systems Pharmacology


Alexander Kulezka Lead


Vanessa Baier: Senior Scientist


Raphaelle Lesage: Scientist


Marco Albrecht: Scientist, Quality Manager


Tanya Zasedateleva: Scientist


Sophie Fischer-Holzhausen: Scientist


Mariana Guimarães: Scientist


Jeremy Perrier: Senior Scientist


Venetia Karamitsou: Scientist

Software


Pavel Balazki: Lead


Ian Peter Du: SW Developer


Diane Lefaudeux: R Dev & Scientist


Felix Mil: Senior SW Dev


Robert McIntosh: Senior SW Eng


Rudolf Engelke: Senior SW Dev


Laura Villain: R Dev & Scientist


Anastasiia Kostiv: SW Developer


Stefano Pizzamiglio: Systems Admin

Systems Toxicology


Marco Siccardi: Lead


Susana Poroenca: Scientist


Stella Fragki: Senior Scientist


Leonie Lautz: Scientist


Lara Lamon: Senior Scientist


René Geci: Doctoral Researcher


Walter Schmitt: Scientific Advisor


Nele Janssen: Office Assistant

Platforms


Huan Yang: qAOP Lead (PS)


Luis Franco: Radiopharm Lead (PS)


Christian Maaß: MPS Lead (PS)


...


Nicoleta Spinu: Training Lead, Scientist


Wilbert De Witte: Biologics Lead (PS)


Carla Troisi: Scientist

- ✓ Our clients range from health-tech StartUps to multinational pharma / chemical companies
- ✓ We strive for **strategic partnerships**

(selected) public-funding R&D collaborations

OPEN SYSTEMS PHARMACOLOGY
www.open-systems-pharmacology.org

esqLABS funded with 480.000 € by

Federal Ministry of Education and Research

CRACK IT
LINK

esqLABS funded with 1600.000+ € by

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

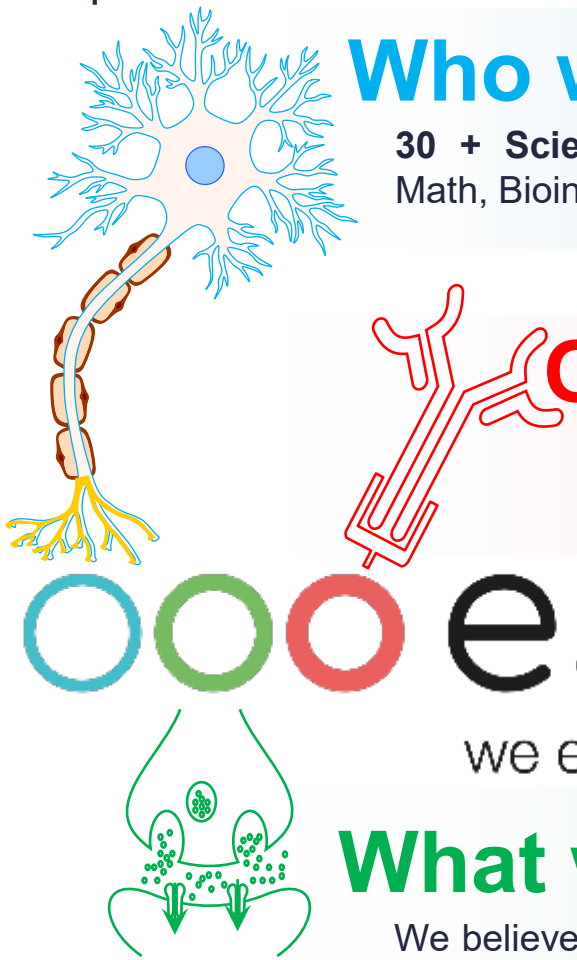
ONTOX
LINK

esqLABS funded with 1.050.000 € by

European Commission

Who We Are

esqLABS at a Glance



Who we are

30 + Scientists with versatile expertise: Control- & Bio Systems Engineering, Pharmacology, Applied Math, Bioinformatics, Software Development, Data Science, Medicine, Biology, Physics and more...

Our expertise

PBP/TK, QSP/T, Disease Modeling, First in Man, (Q)IVIVE, IVIVC, Special Populations, Virtual Bioequivalence, Tox Risk Assessment, Machine Learning, Data Analysis, and much more...

esQlabs

we empower life sciences

What we believe in

We believe in the power of knowledge-based, mechanistic models based on an open-source and open-science approach with **open-source software as a foundation for advancing innovative and impactful work** in science, education, and industry which is why we help develop and sustain it.

02

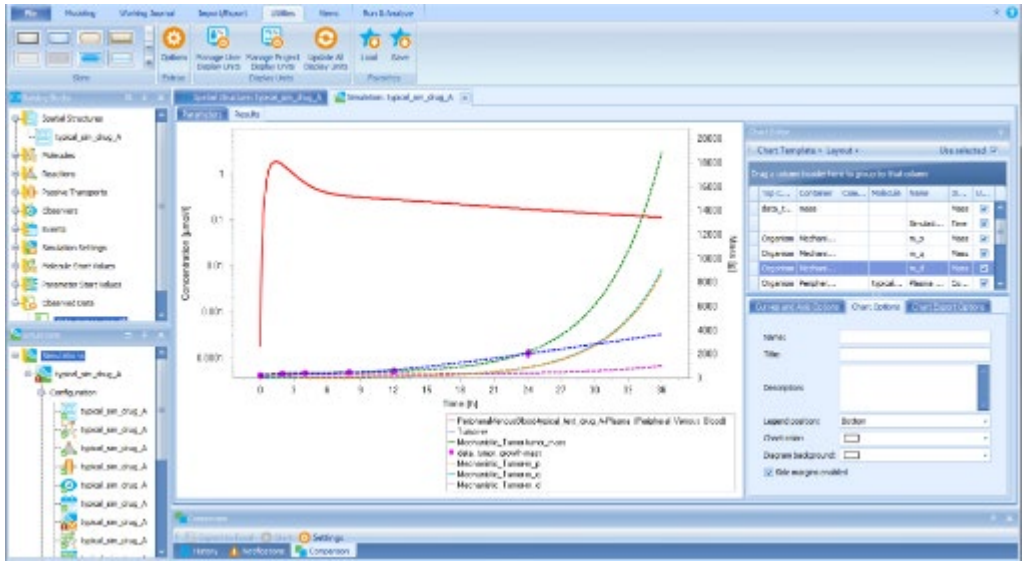
OSP Software

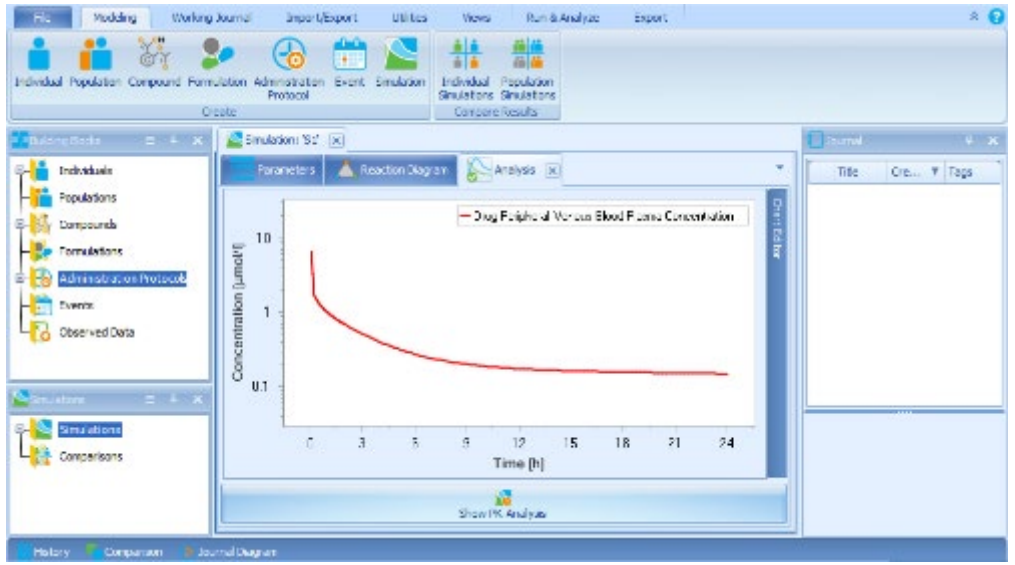
Modeling with PK-Sim® and MoBi®

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**!

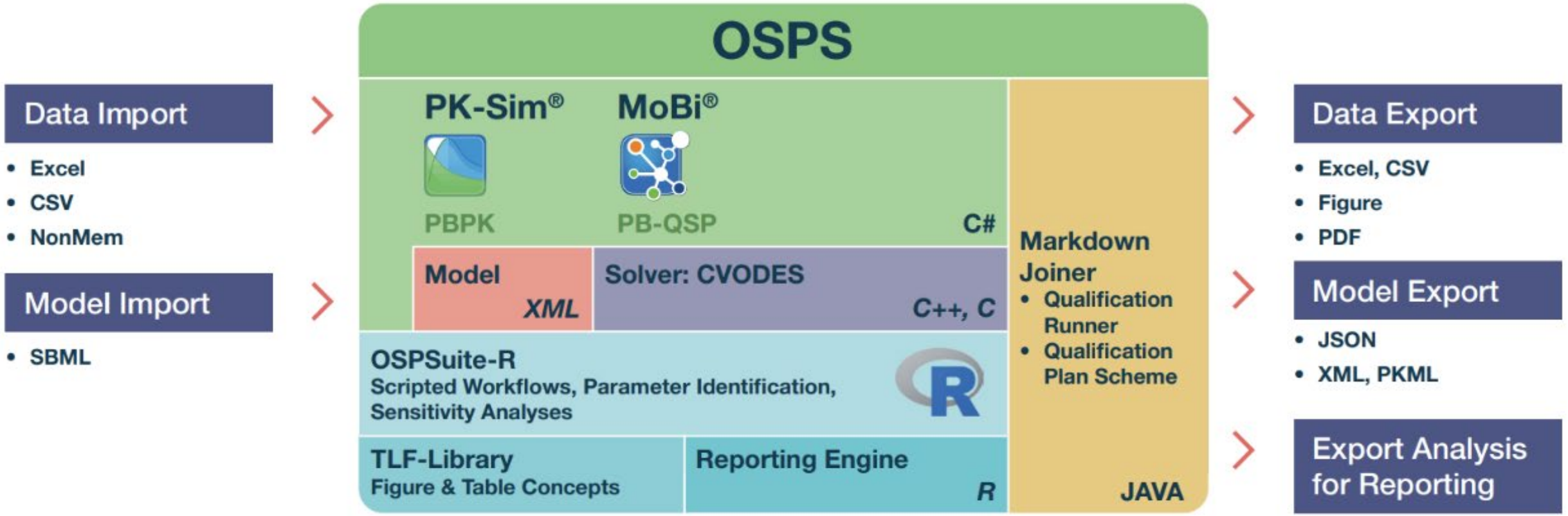
MoBi® & PK-Sim® = OPEN SYSTEMS PHARMACOLOGY





OSP Suite (PK-Sim® & MoBi®): Platform concept

Integration of PBPK/PD with other platform components

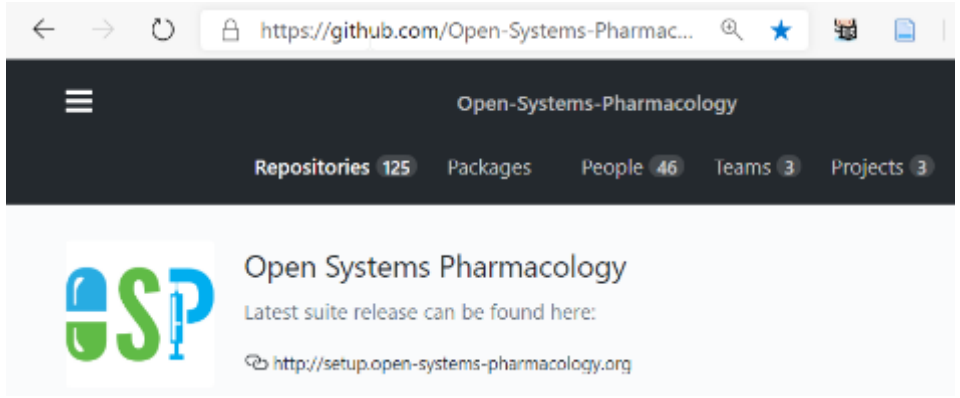


Open Systems Pharmacology (OSP)

www.open-systems-pharmacology.org

Open-Source PBK & QSP/T Software Project

Stakeholders of the **Open Systems Pharmacology** community and **Management Team**



Open Source since 2017 at Github

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

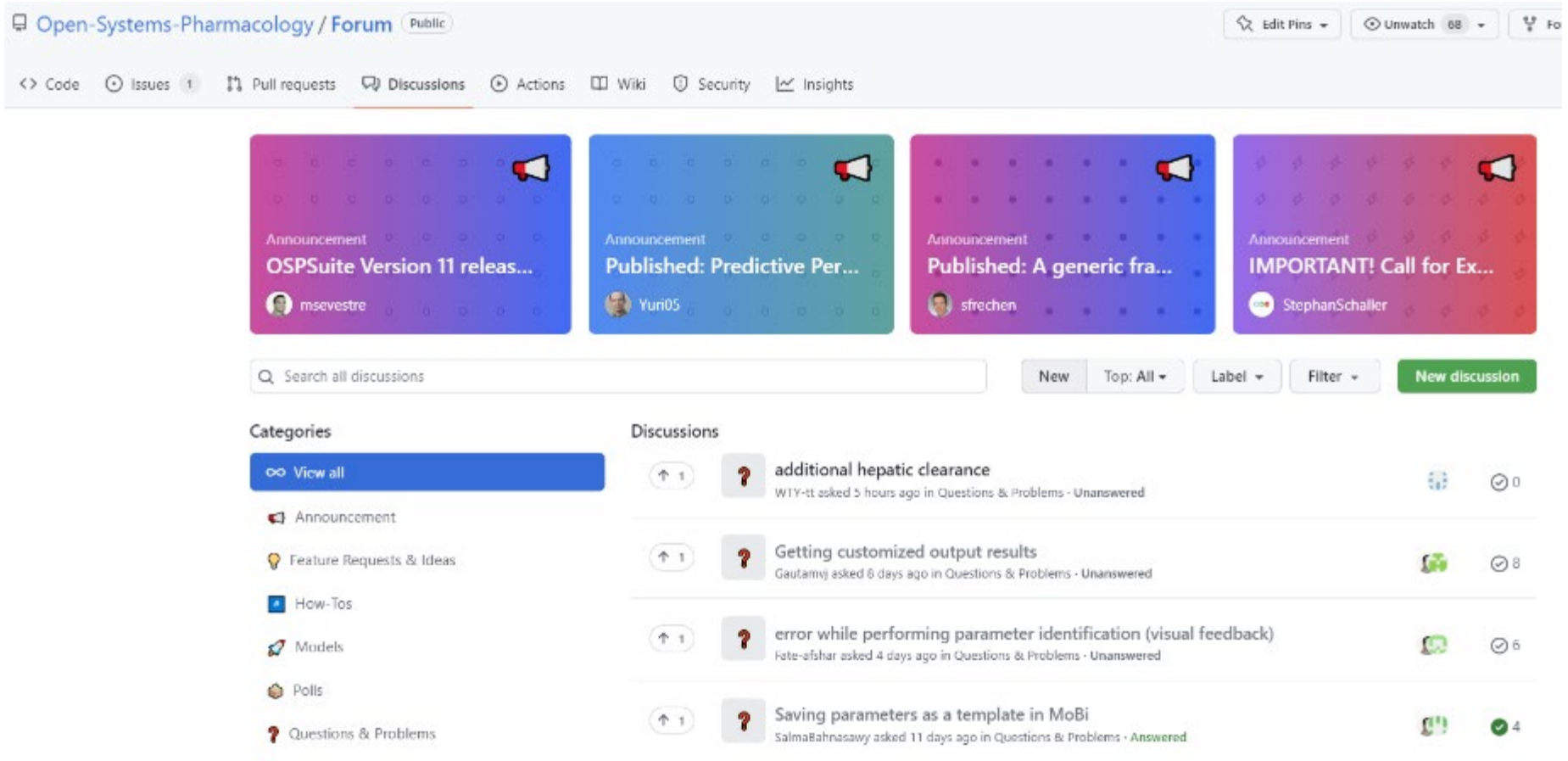
http://www.open-systems-pharmacology.org/

Community, Roadmap, and Focus Groups

Community: Forum (github.com/Open-Systems-Pharmacology/Forum)

FORUM

Have your questions answered or provide answers to others. The Forum is a great way to stay up-to-date on the community buzz around OSP.



Community, Roadmap, and Focus Groups

Roadmap: https://github.com/Open-Systems-Pharmacology/Roadmap

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.

Community, Roadmap, and Focus Groups

Focus Groups

- 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

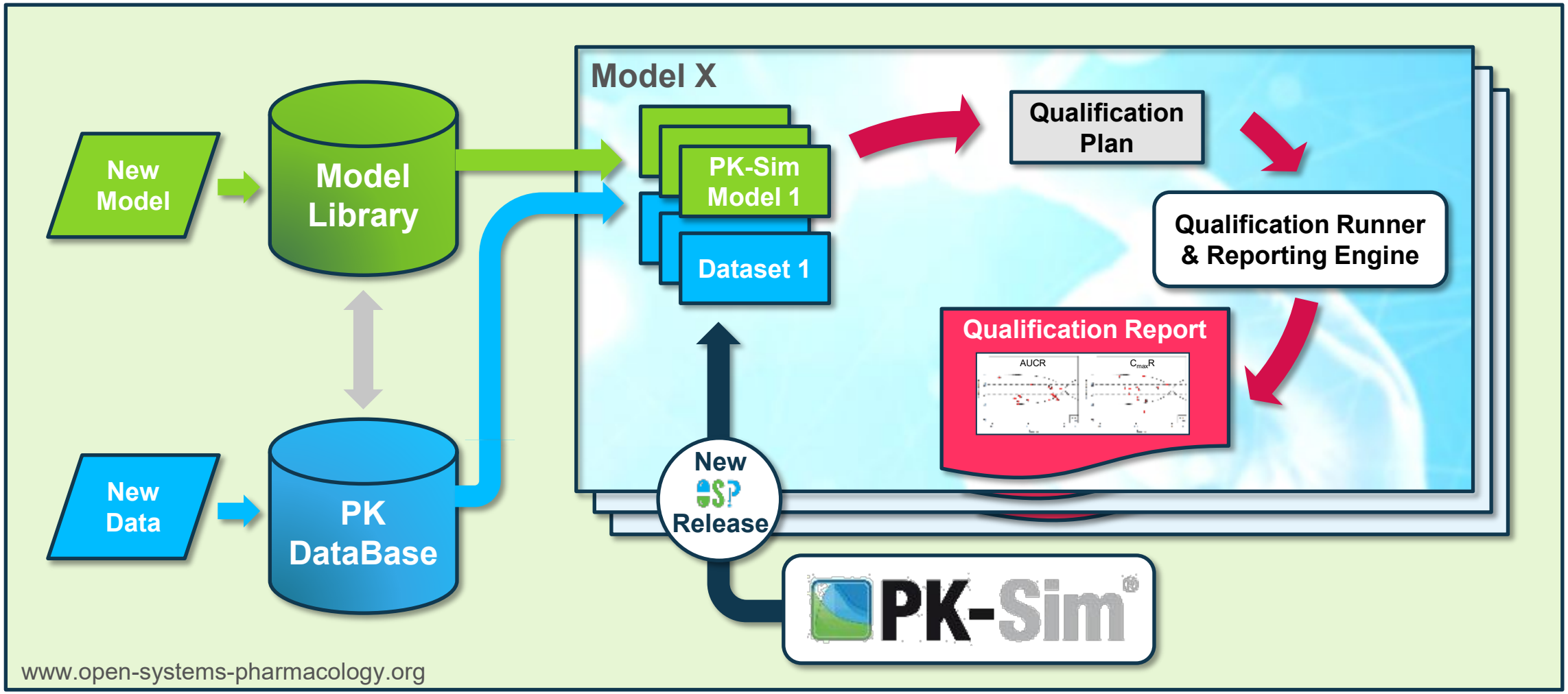
Dedicated Focus Groups have been established to conceptualize, design and progress the individual areas, the Management Team will coordinate the interplay of focus areas and interfaces between them

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 • Provide guidelines on how to conduct IVIVE in PK-Sim • Facilitate integration of in vitro data in prediction of DDI (e.g. integration of fraction metabolized) • 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 1. technical generation of populations destined for the OSP Suite and, 2. evaluation of those populations. 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)

Automatic (Re)-qualification Workflow

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



FDA's white list of file formats for electronic submissions

OSP file formats are added to the list for electronic submissions

- The following OSP file formats are included:
  - **.pksim5** (PK-Sim project file)
  - **.mbp3** (MoBi project file)
  - **.pkml** (OSP model exchange format)
  - **.json** (PK-Sim project snapshots file)

Specifications for File Format Types Using eCTD Specifications

Revision History

Date	Version	Summary of Changes
2023-12-01	9.0	Updated .docx permissible uses Updated .xml accepted locations and permissible uses Removed "CDER Only" from permissible uses for: .csv, .cas, .dat, .rmd, .r Updated file format added: Modeling & Simulation file types: .pksim5, .mbp3, .pkml, .json, .mlxtran, .mlxproperties, .pkx, .pkxproperties, smlx, .smlxproperties, .syc, .datxplore

https://www.fda.gov/media/85816/download

OSP Suite (PK-Sim® & MoBi®):

Flexible ODE-based M&S environment

- Anything, that can be described by an ordinary differential equation (ODE) system can be modeled & simulated

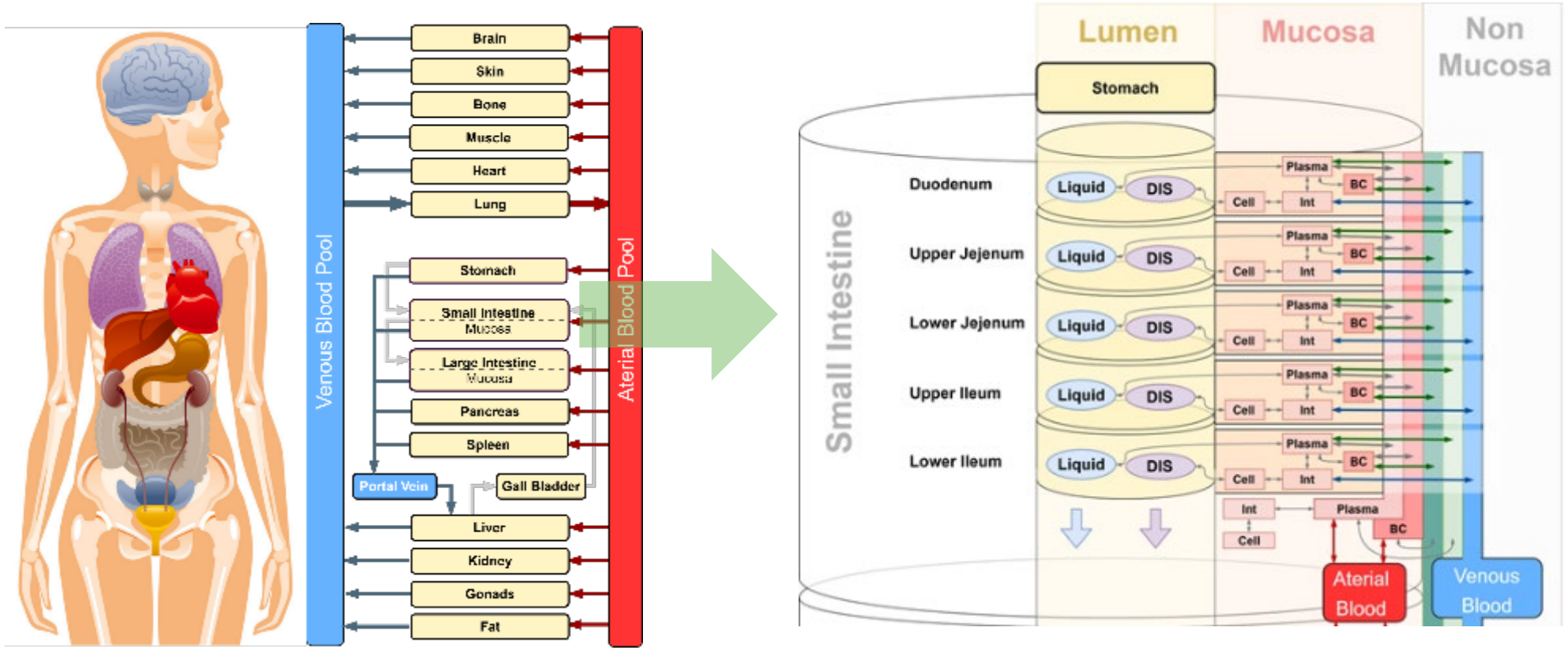
$$\dot{x} = f(x, p)$$

03

PBPK for Oral Absorption

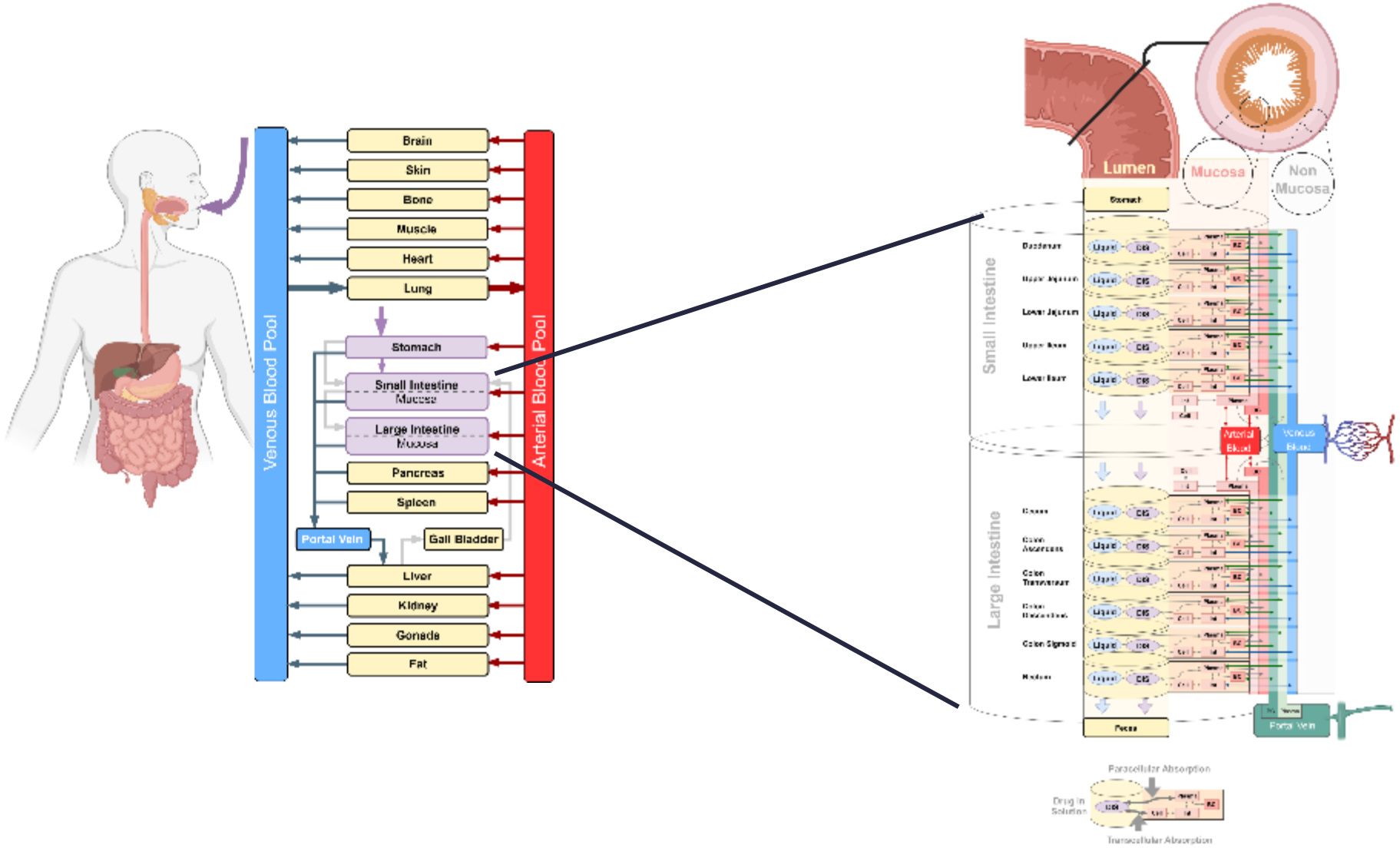
Modeling with PK-Sim®

Multi-Compartmental Gastro-Intestinal (GI) Model



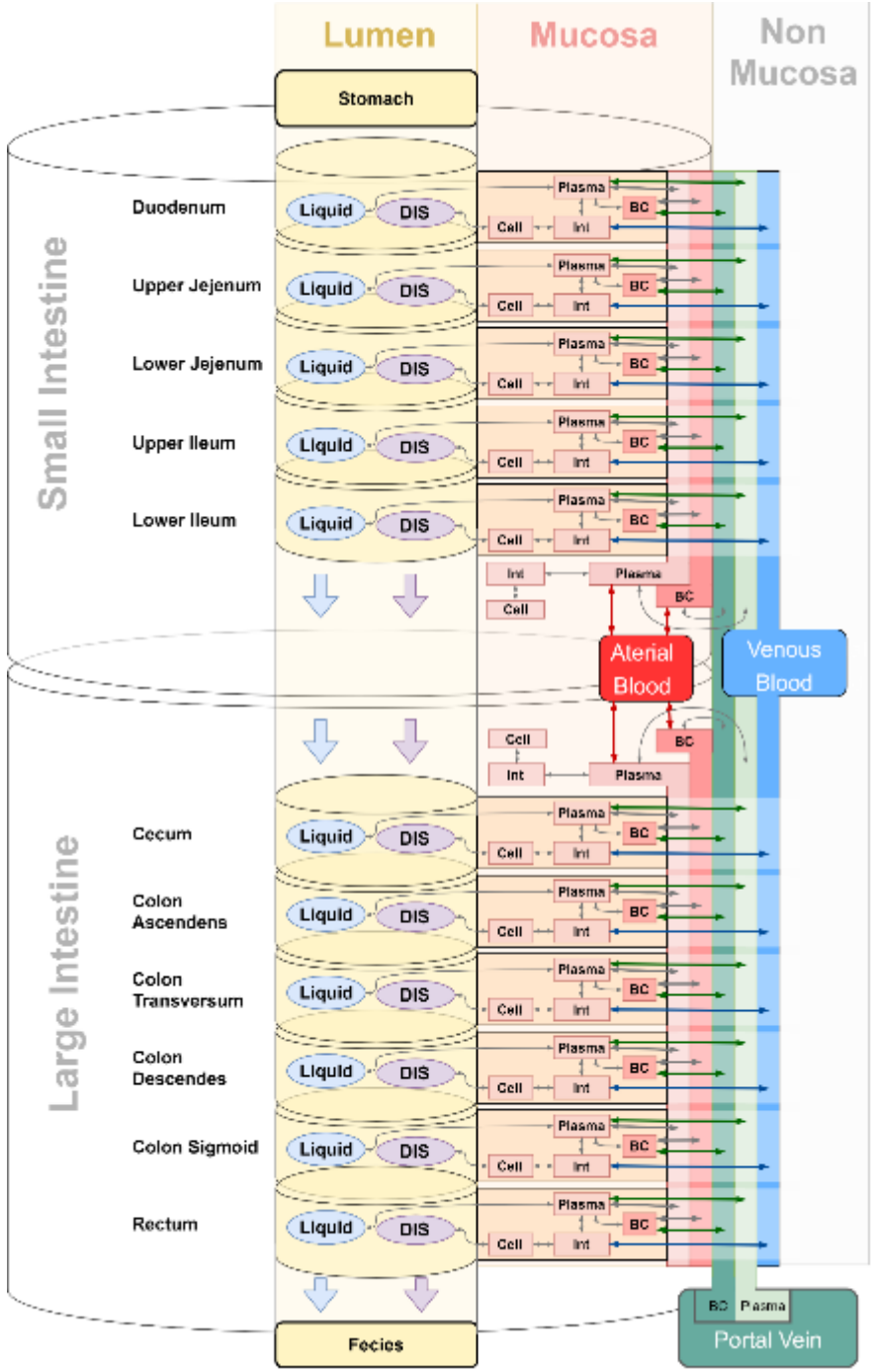
- Basic PBPK model structure implemented in PK-Sim® and detailed model structure of the gastrointestinal tract. For better visualization, the large intestine is not shown.

Oral Absorption in the OSP-Suite



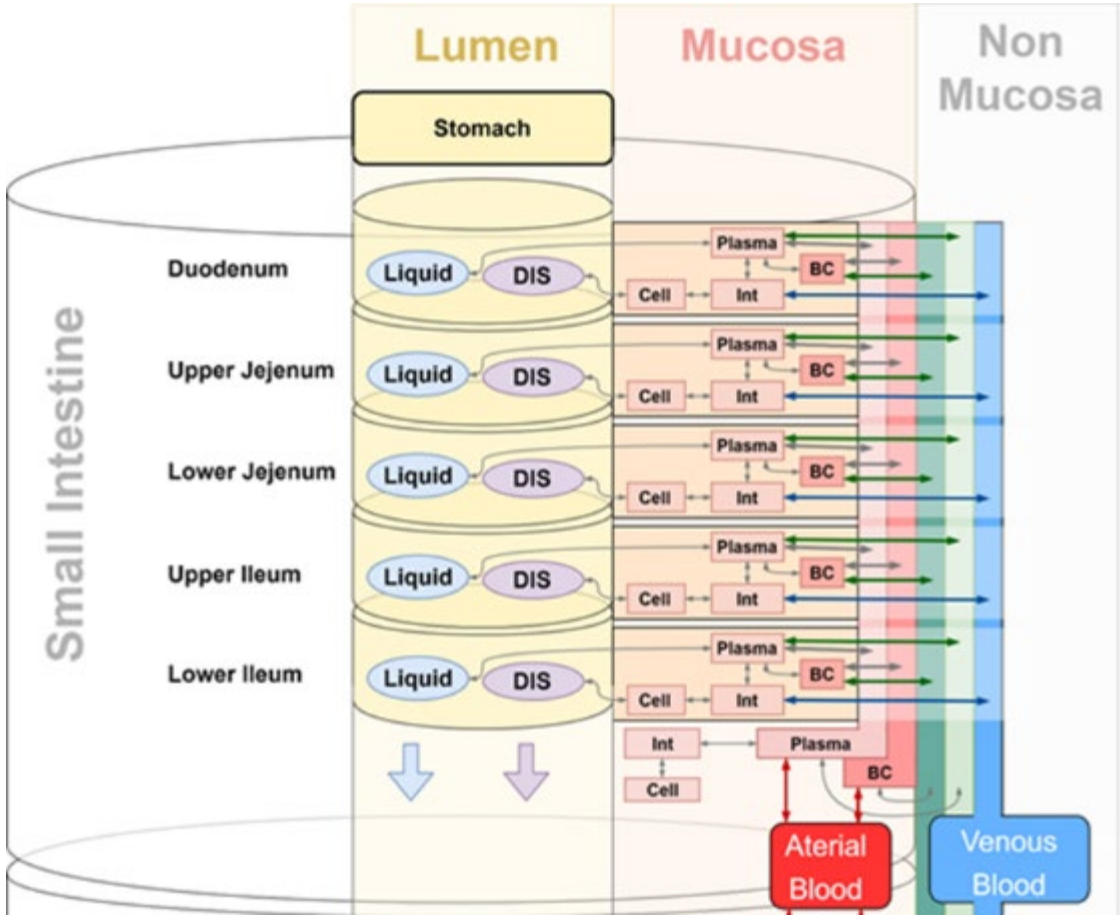
Multi-Compartmental Gastro-Intestinal (GI) Model

- 12 compartments representing the lumen of the GI tract from stomach to rectum
- Varying properties:
  - Dimensions
  - pH values
  - absorptive surface area
  - transit times
- 11 compartments representing the intestinal mucosa:
  - subdivided into enterocytes, interstitial and vascular space
- Explicit representation of intestinal mucosa allows to account for
  - CYP distribution
  - transporter distribution



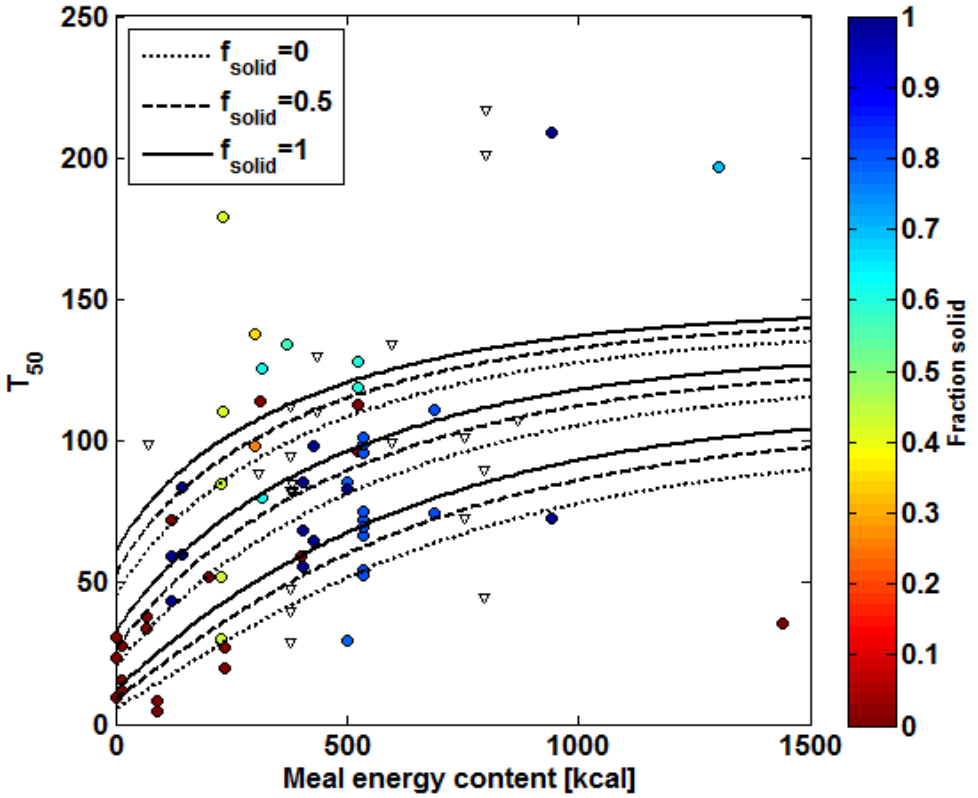
Multi-Compartmental Gastro-Intestinal (GI) Model

- Each segment contains physiological liquid volumes (Liquid) and drug in solution (DIS)
- Solid dosage form (SDF, e.g. Tablet) is transported along the GI tract independently
- Once released from SDF and dissolved according to the dissolution function, the drug is transferred from the SDF species to the DIS species



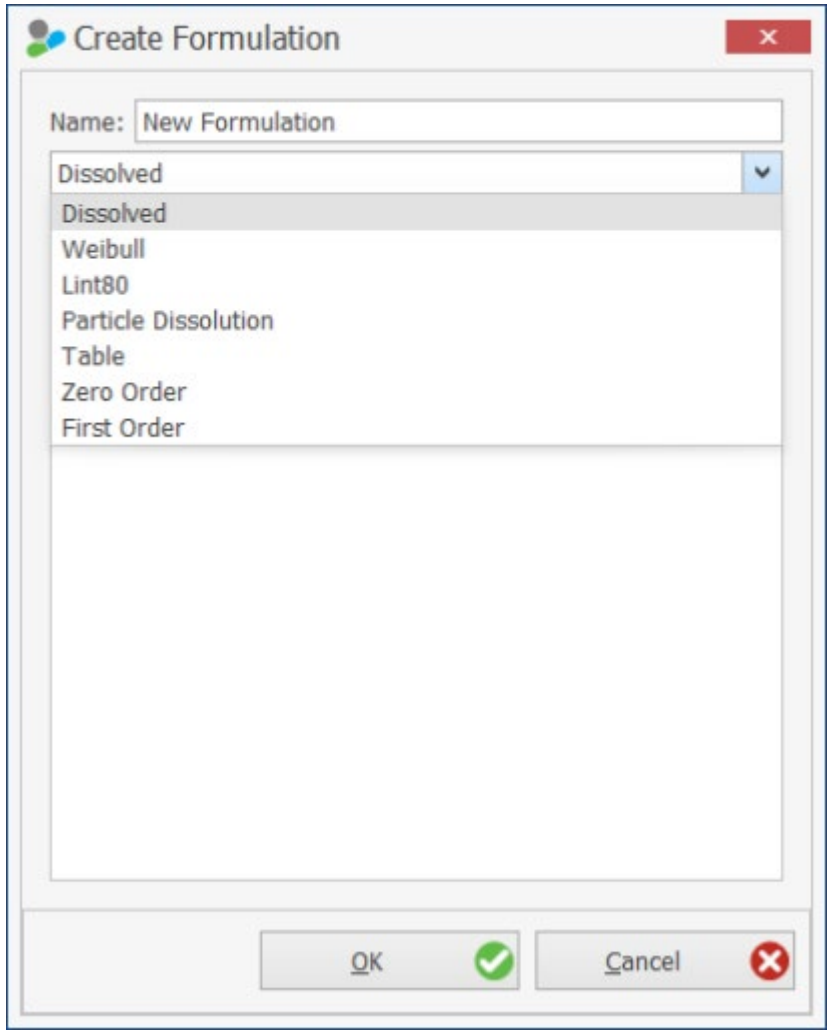
Events in PK-Sim: Meal Effect

- Food can influence drug absorption through different physicochemical and physiological mechanisms
- One important factor is the rate of gastric emptying (GE)
- In PK-Sim, a function is implemented that describes the relationship between the characteristics of a meal and the GE rate



Relationship between T50, meal energy content and meal composition in terms of solid components.

Formulations in PK-Sim



- Dissolved: Solution or immediate release formulation without limitation due to dissolution process
- Weibull: empirical dissolution function enabling to fit almost any kind of dissolution curve; the Weibull function expresses the accumulated fraction of the drug (m) in solution at a time t

$$m = 1 - \exp\left[\frac{-(t - T_{\text{lag}})^b}{a}\right]$$

- Table: enables the upload of in vitro dissolution data
- Lint80, Zero Order, First Order: empirical functions

Literature example: Biphasic dissolution

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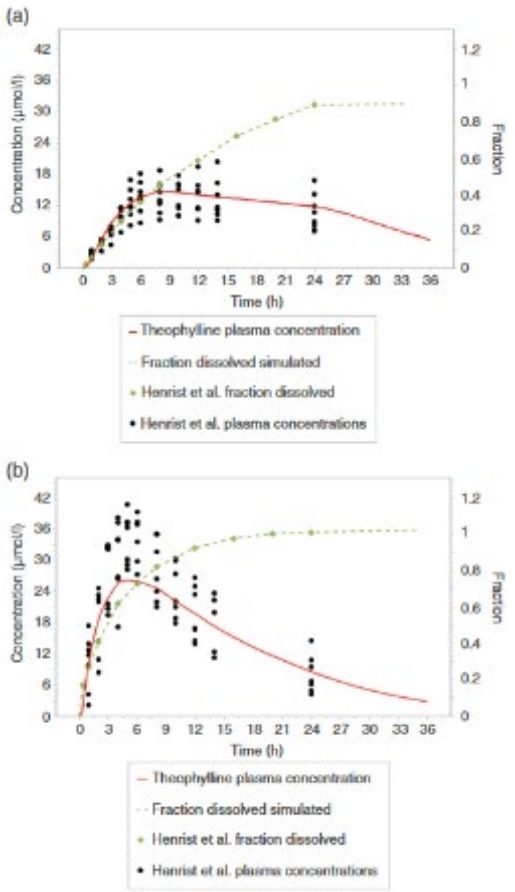
PK-Sim® for Modeling Oral Drug Delivery of Modified-Release Formulations

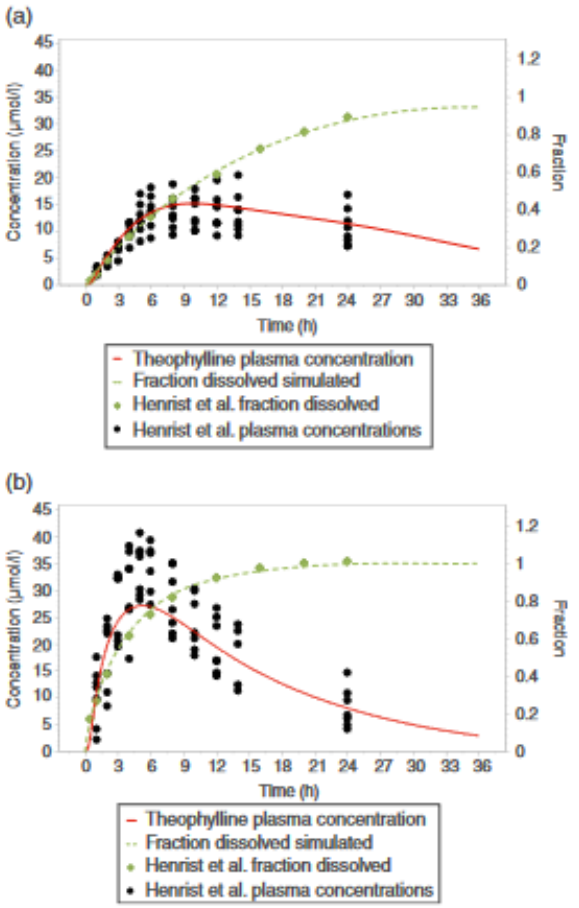
Donato Teutonico[1,2], Michael Block[1], Lars Kuepfer[1], Juri Solodenko[1], Thomas Eissing[1], and Katrin Coboeken[1]

[1] *Clinical Pharmacometrics, Bayer AG, Leverkusen, Germany*
[2] *Translational Medicine and Early Development, Sanofi R&D, Chilly-Mazarin, France*

- Theophyline plasma concentration data for two formulations can be described by using the observed in vitro dissolution profile directly or by fitting a Weibull

	Xanthium capsule	Hot stage extrusion formulation
Dissolution time (50% dissolved)	155 min	540 min
Dissolution shape	0.83	1.11

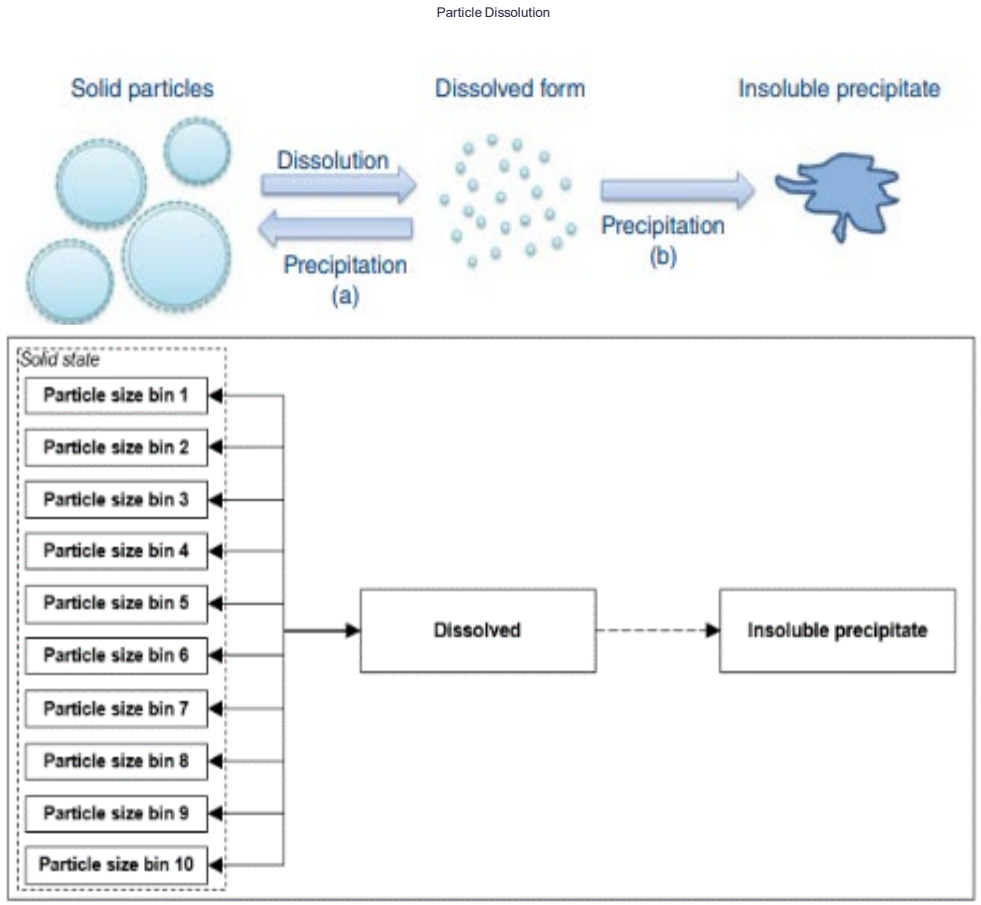




A special case: the particle dissolution model

Setting up a formulation

- Multiple Properties
  - Mono- and Polydisperse
  - Distribution type
  - Particle Sizes (mean, SD, min, max)
  - Thickness Unstirred Water Layer
- “Enable supersaturation”: dynamic precipitation as the drug transits.



A special case: the particle dissolution model

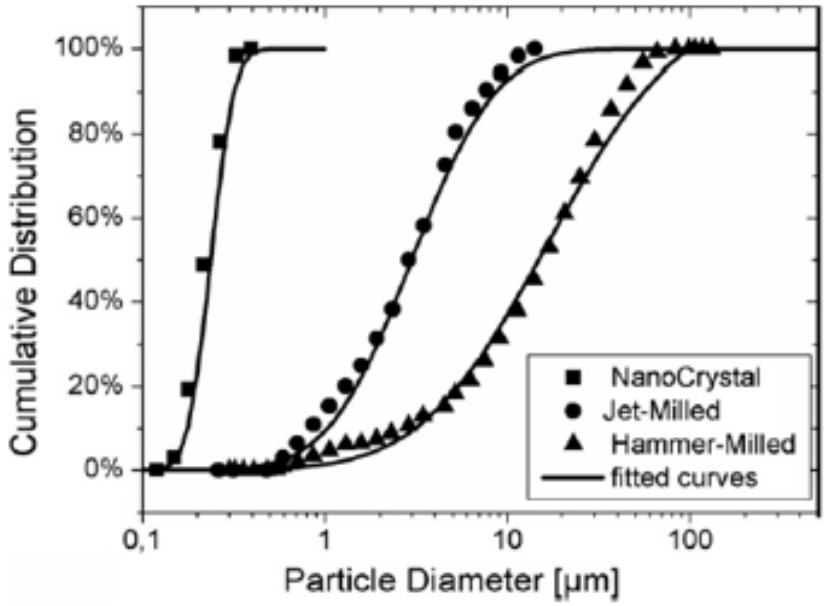
Real-life example

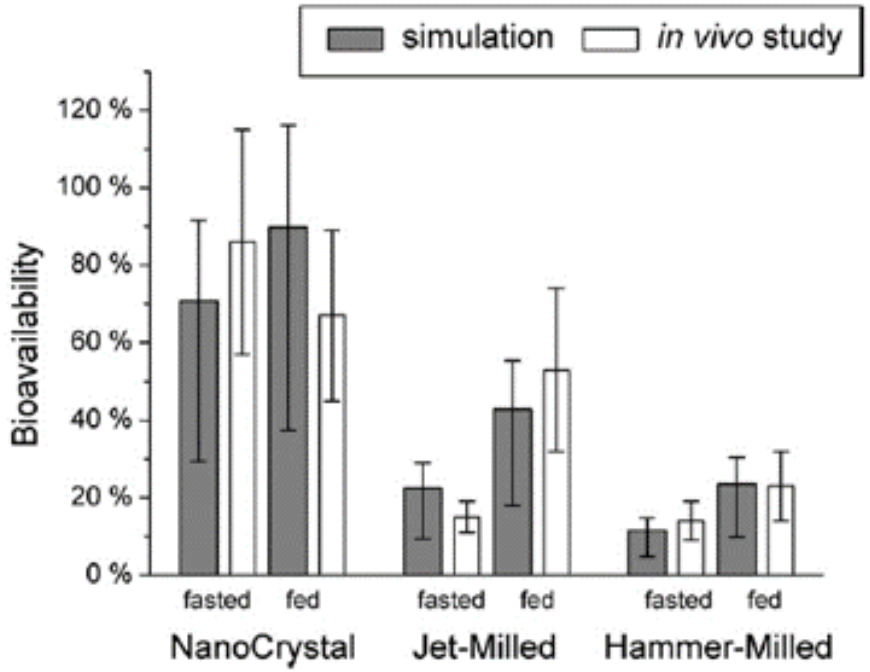
Research paper

Mechanism-based prediction of particle size-dependent dissolution and absorption: Cilostazol pharmacokinetics in dogs

Stefan Willmann [a,*], Kirstin Thelen [a,b], Corina Becker [a], Jennifer B. Dressman [b], Jörg Lippert [a]

[a] Bayer Technology Services GmbH, Competence Center Systems Biology and Computational Solutions, Leverkusen, Germany
[b] J.-W. Goethe University, Institute of Pharmaceutical Technology, Frankfurt a.M., Germany





A special case: the particle dissolution model

IVIVC workflow with hypothetical data

Example of OSP flexibility and community support - IVIVC with the particle dissolution module implemented in OSP

Detailed description on GitHub

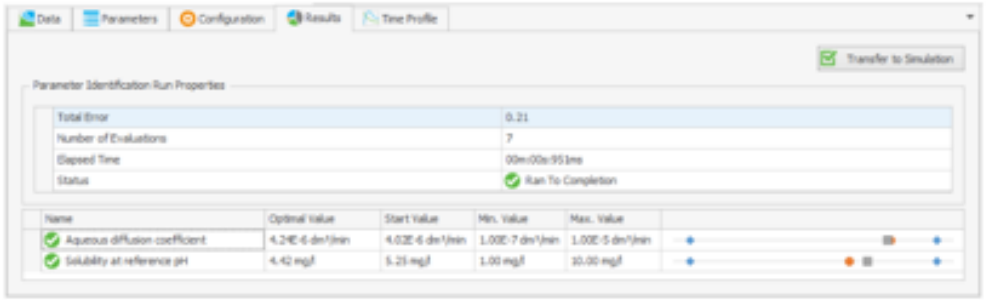
Open-Systems-Pharmacology/IVIVC-with-particle-dissolution-module-in-OSP (github.com)

Workflow

The workflow for establishing IVIVC with OSP comprises the following three consecutive steps:

1. Fitting a cumulative distribution function to a distribution of measured particle sizes using R
2. Fitting the particle dissolution function to *in vitro* dissolution profiles measured in biorelevant media using MoBi®
3. Transferring the particle size distribution from step 1 and parameters of the dissolution function from step 2 to PK-Sim® for predicting dissolution in the gastrointestinal tract *in vivo*

Step-by-step instructions with screenshots



3. Transfer particle size distribution and particle dissolution parameters to PK-Sim®

In this step, the discretized particle sizes generated in step 1 and the parameters of the particle dissolution function from step 2 will be transferred to PK-Sim® for predicting dissolution in the gastrointestinal tract *in vivo*.

A special case: the particle dissolution model

IVIVC workflow with hypothetical data

Example of OSP flexibility and community support - IVIVC with the particle dissolution module implemented in OSP

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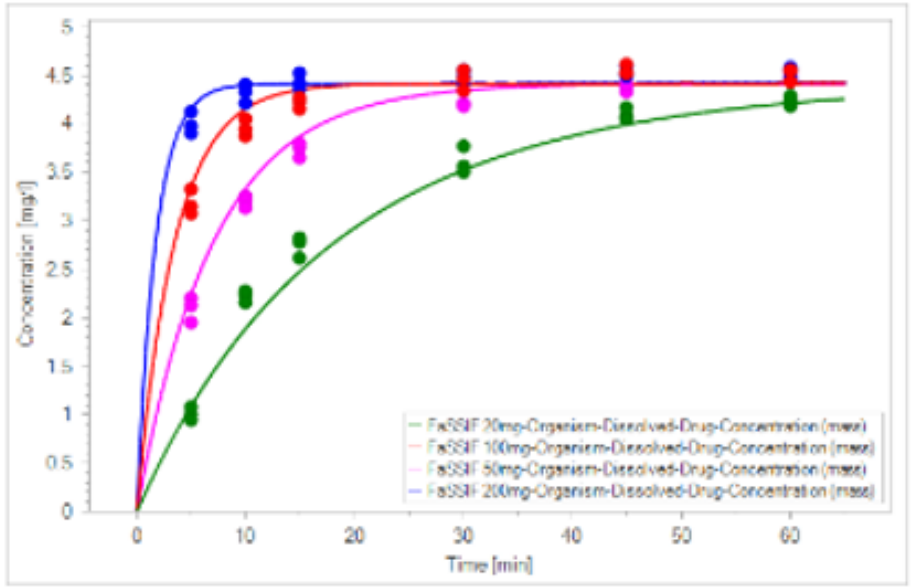
Fitting results of hypothetical in vitro dissolution data



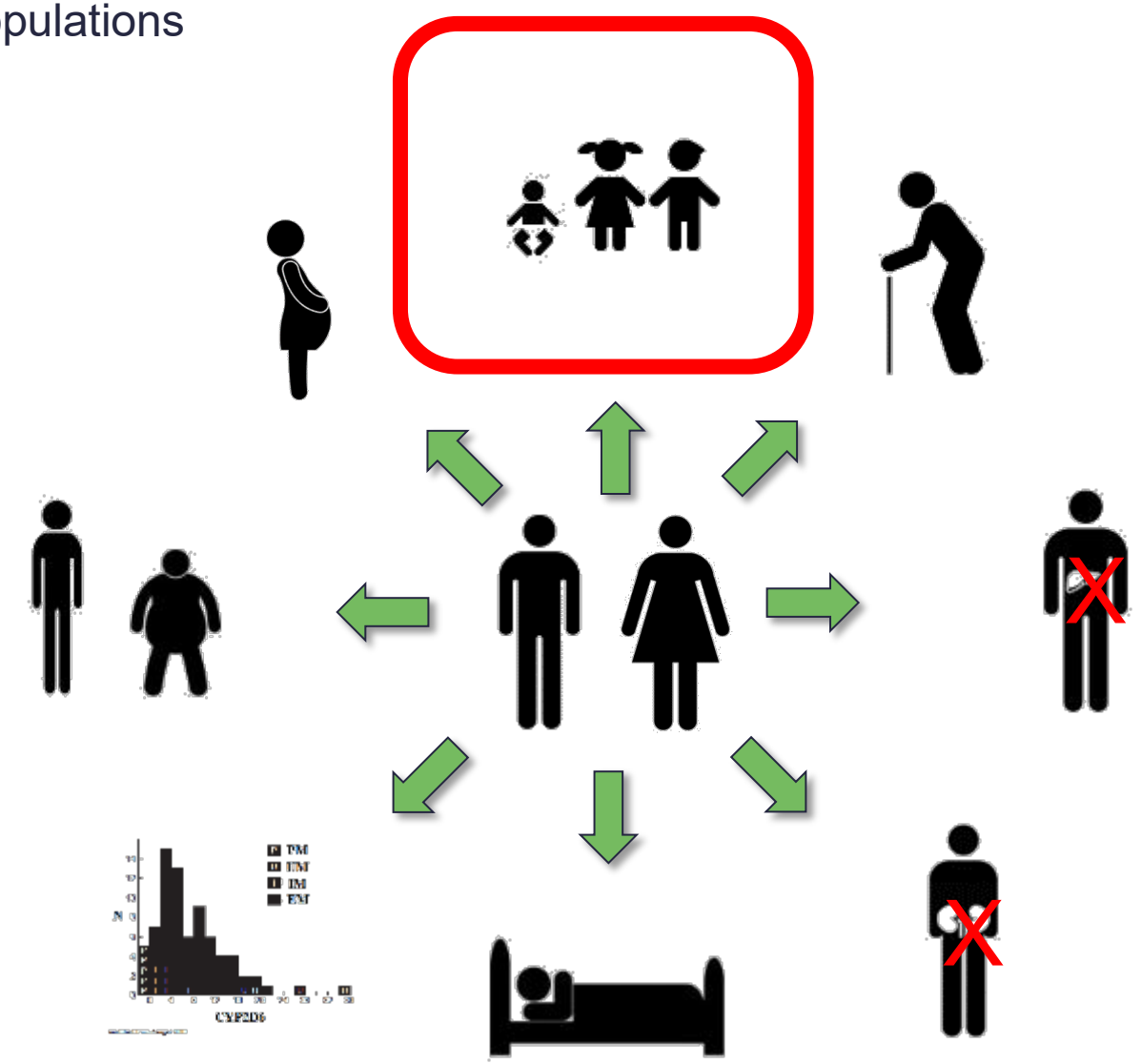
04

PBPK for Pediatrics

Modeling with PK-Sim®

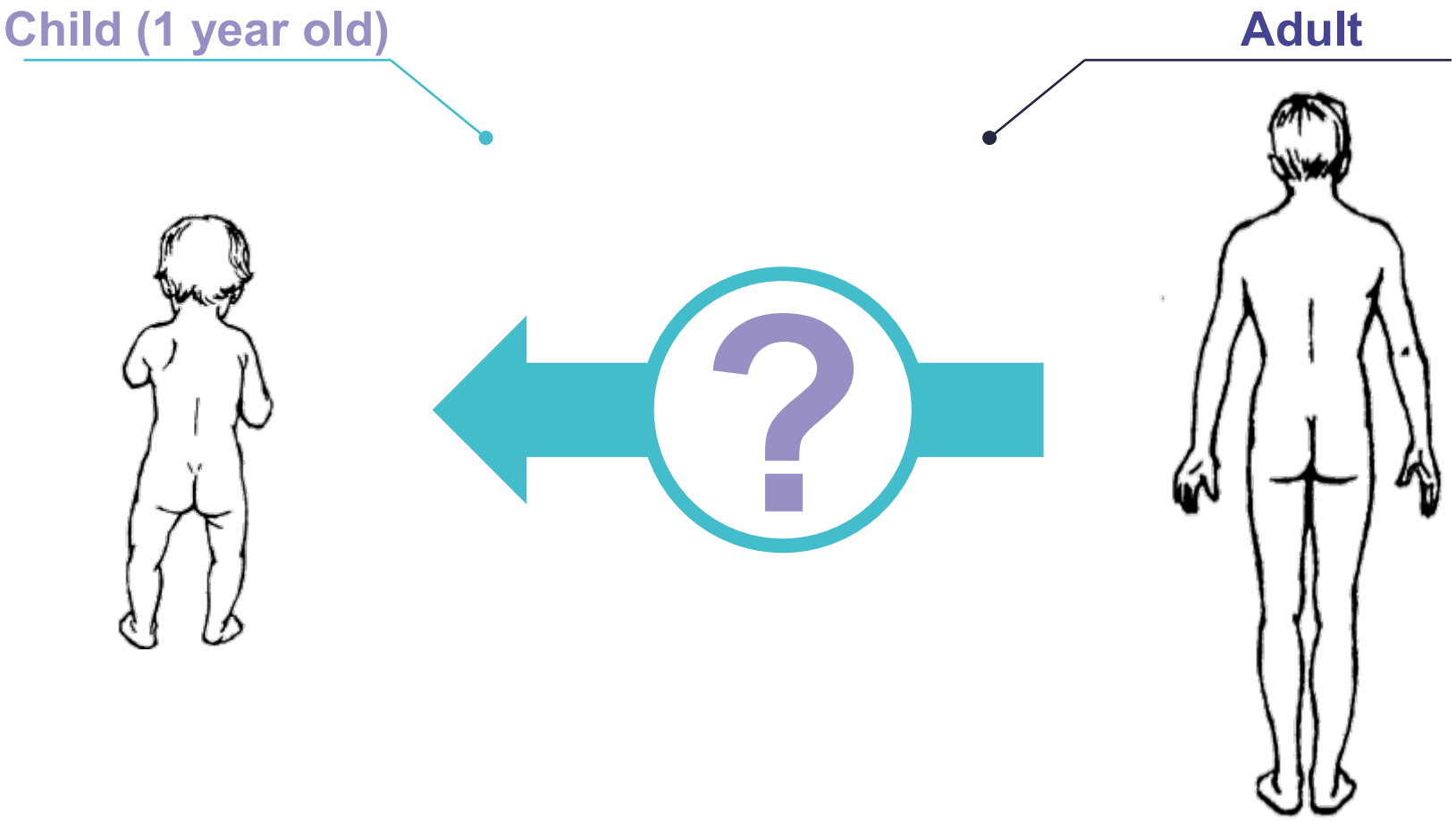
PBPK Modeling | The Physiological Database

Overview – special populations



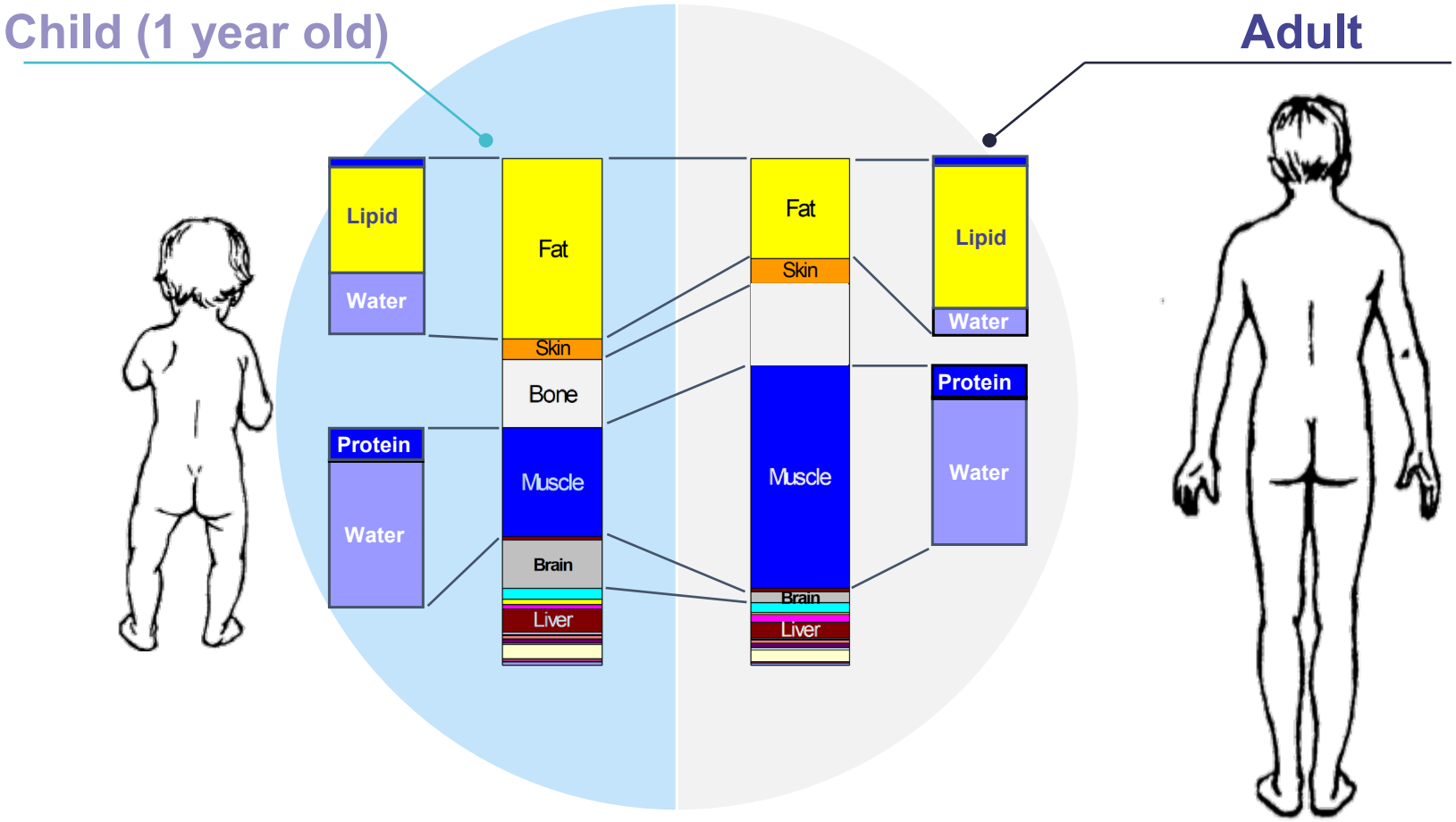
Bridging from adults to children

What information do we need?



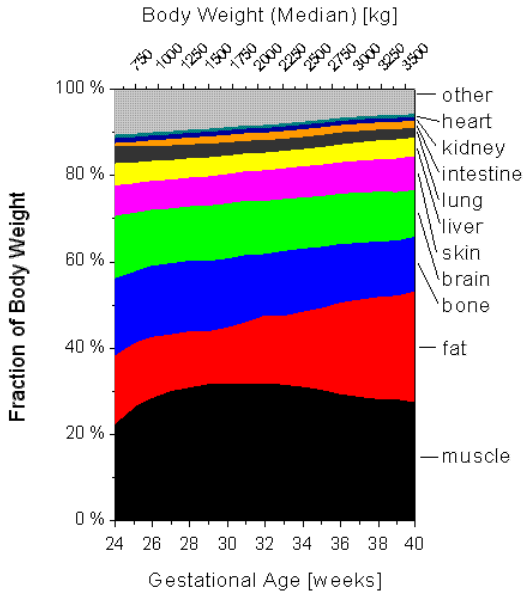
Bridging from adults to children

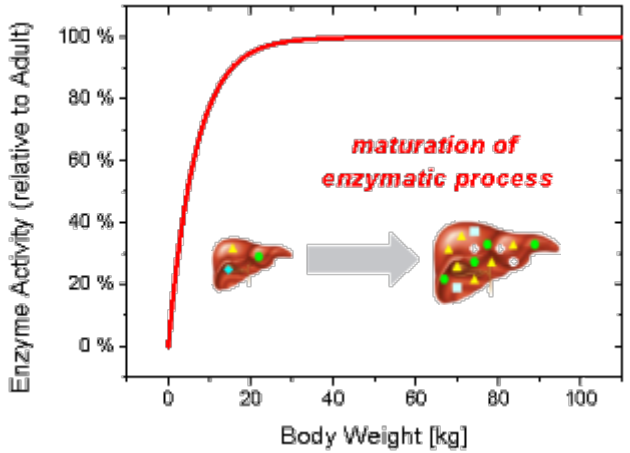
What information do we need?

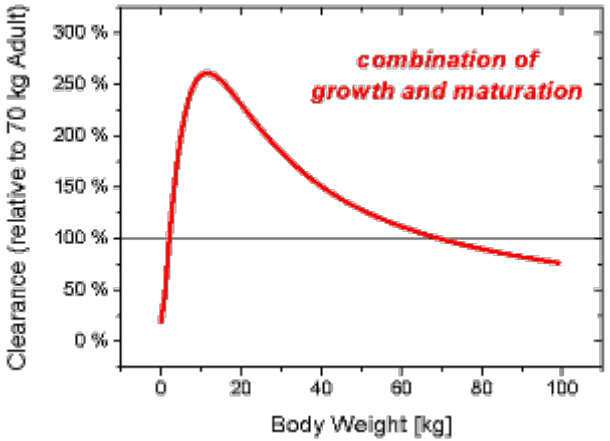


The Physiological Database

Age-dependency of clearance processes





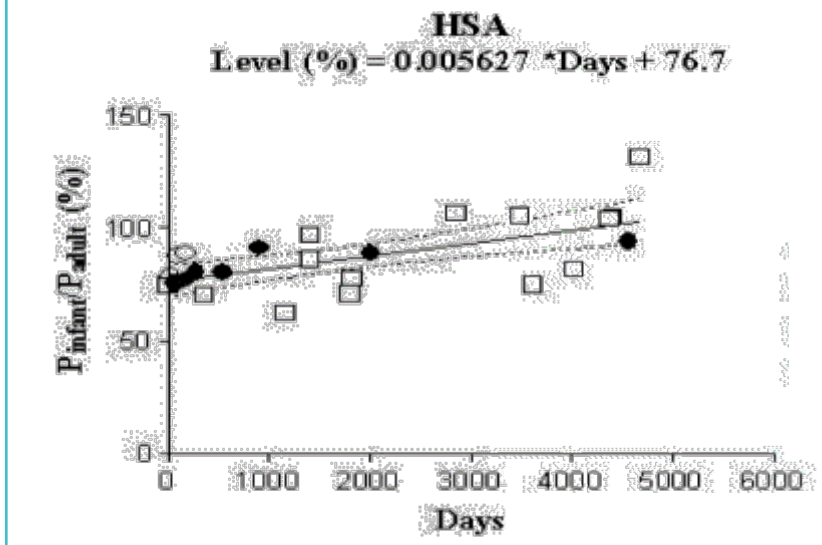


The Physiological Database

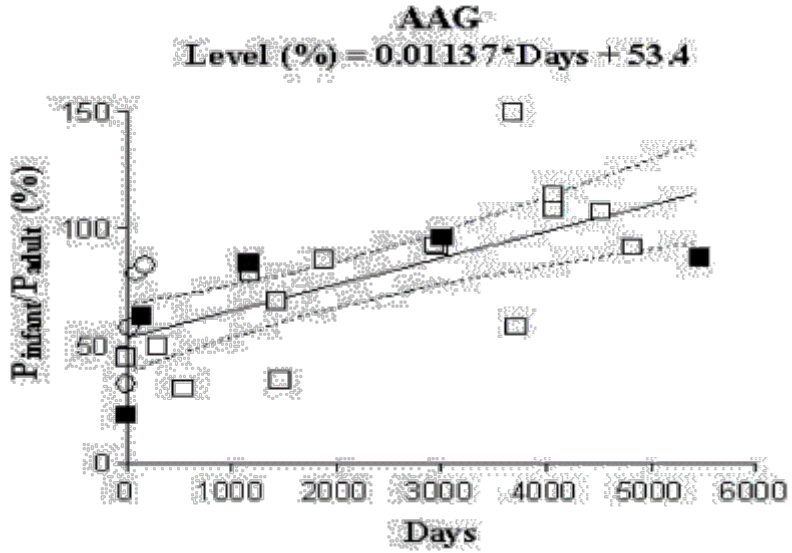
Age-dependency of clearance and excretion

- Adult levels are reached at around 11 years of age
  - Lower plasma protein levels in young children compared to adolescents and adults affect drug distribution and elimination

serum albumin



α-glycoprotein



McNamara and Alcorn, AAPS PharmSci (2002)

The Physiological Database

Protein ontogeny database

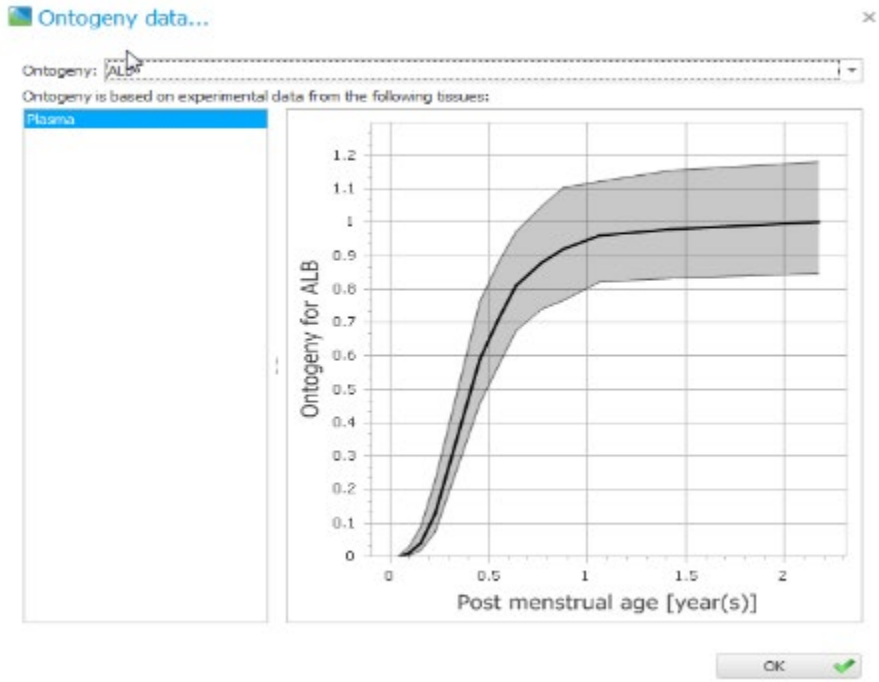
- Literature data to the age dependent expression of proteins influencing the ADME properties of drugs (enzymes, transporters, binding partners) were **(re)evaluated**

- **Fit to data** using a maturation model based on a sigmoidal Emax model (corresponding to the Hill-equation):

$$A = PMA^n/(A_{0.5}^n + PMA^n)$$

PMA	= Postmenstrual age
A	= Activity at PMA
A0.5	= PMA at 50 % activity compared to adult
n	= Hill coefficient

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



Workflow For Scaling Pharmacokinetics

From adults to children using PBPK

Step 1:

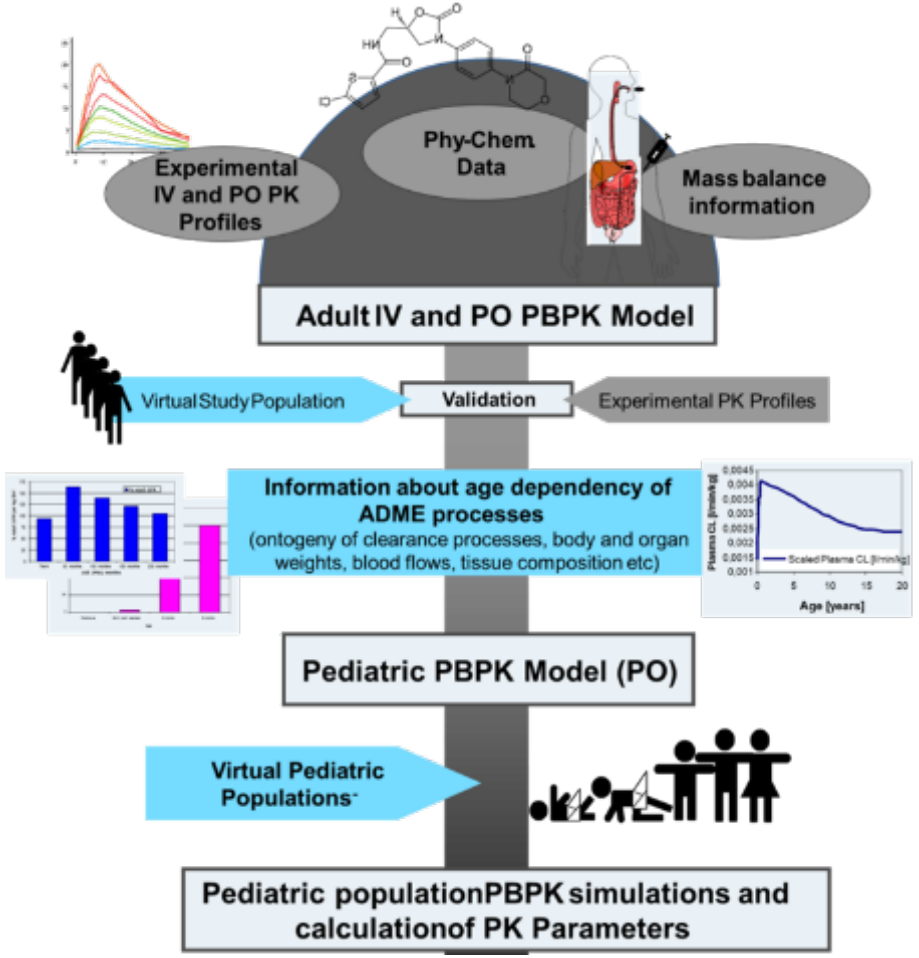
Development and validation
of a PBPK Model for adults

Step 2:

Scaling 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



Edginton et al., Clin. Pharmacokin. (2006)

Paediatric PBPK | Case example Rivaroxaban

Rivaroxaban – oral anticoagulant medication

- Direct, specific, competitive FXa inhibitor
- Inhibits free and fibrin-bound FXa activity, and prothrombinase activity
- Inhibits thrombin generation – acts earlier in the coagulation cascade
- Predictable pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects
  - Reaches Cmax in 2.5–4 hours
  - Half-life of 5–9 hours at steady state
  - Low intra-individual variability: 8–13% for AUC, 11–18% for Cmax
  - Moderate inter-individual variability: 26–41% for AUC, 21–33% for Cmax
  - Multiple pathways of elimination: 2/3 metabolism and 1/3 renal excretion
  - No major circulating metabolites

Paediatric PBPK in PRETERMS

The “very special” population

- Up to 93% of preterm born neonates in ICU care receive at least one unlicensed and/or off-label use of a drug.
- Rapid developmental changes in neonates strongly impact PK of drugs
- A PK-Sim® preterm model was established, which describe rapid developmental changes in preterm born neonates (Blei et al., in press)

Courtesy of www1.wdr.de

05

Examples

Pediatric Drug Development

Regulatory Submissions for Pediatrics

Examples I (FDA Submission)

- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/209529Orig1s000ClinPharmR.pdf
- Sponsor: **Astellas Pharma US, Inc.**
- CRO: -
- Indication: Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older
- "*Solifenacin PBPK models were developed using the PK-Sim® v5.1 to describe the clinical plasma PK profiles of solifenacin in adult and pediatric populations*"
- PBPK was used to:
  - Define the dosing regimen for the pediatric population

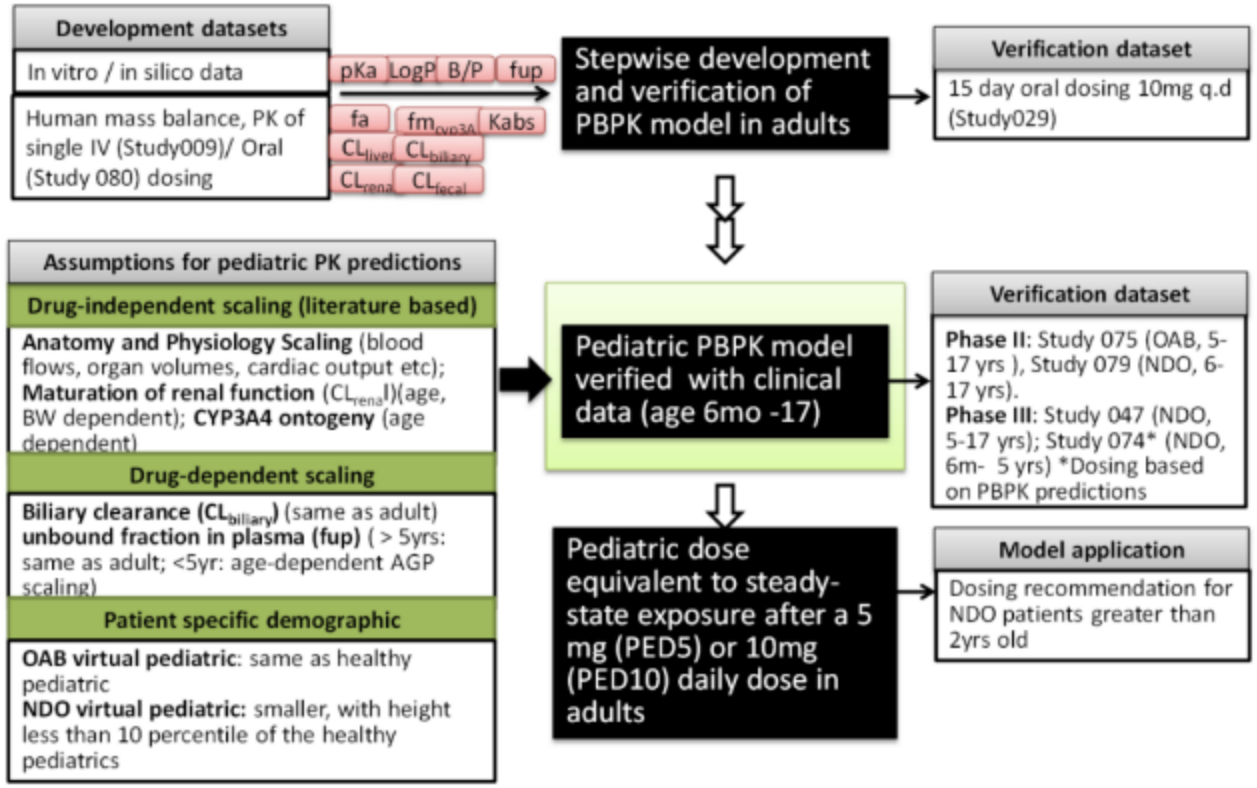
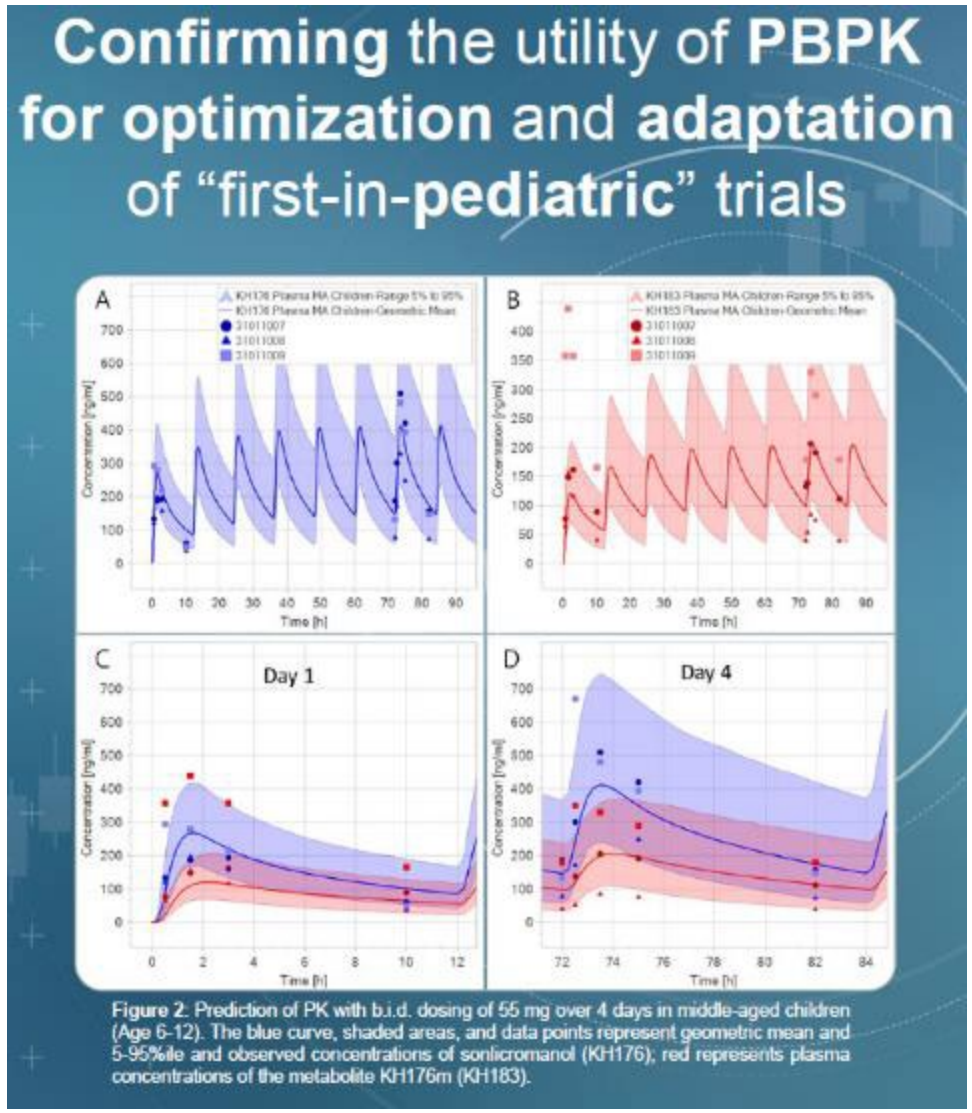


Figure 4.2- 1 Workflow of development, verification and application of solifenacin PBPK models

Regulatory Submissions for Pediatrics

Examples II (Submission to EMA (PDCO))

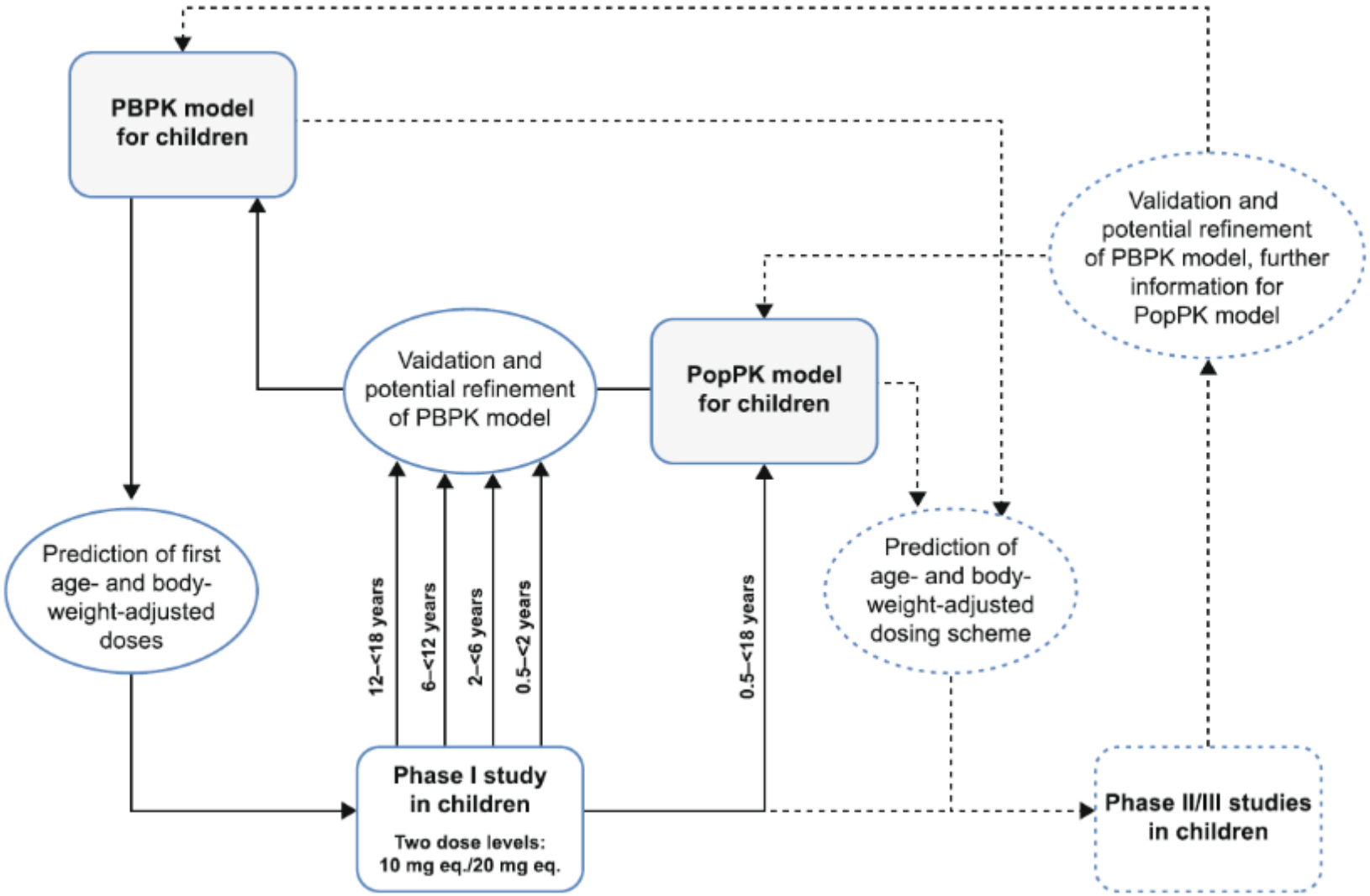
- (Poster, manuscript in preparation)
- Sponsor: **Khondrion BV**
- CRO: ***esqLABS GmbH***
- Indication: mitochondrial disorder
- "***PK-Sim V9.1*** *(Open Systems Pharmacology) was used by the Applicant for a PED study design to develop the PBPK models pediatric PK predictions, dose optimization and sampling schemes.*"
- PBPK was used to:
  - Predict exposure of a CYP3A4 and P-gp substrate and optimize a pediatric equivalent dose (PED, based on AUC) for neonates and up to the adolescent age range
  - Used PK-Sim and R to derive an optimal sampling schedule for the different age groups.
  - Use of PK-Sim in an adaptive trial design to re-evaluate and (if required) re-calculate the optimal dose in children
  - **Used & referenced (off-the-shelf, i.e. From GitHub) qualified enzyme ontogenies for CYP3A4 and P-gp (P-gp pending final upload)**



Paediatric PBPK | Case example Rivaroxaban

Workflow for scaling PK using PBPK

- Sponsor: Bayer Pharmaceuticals
- Workflow for PBPK and PopPK modelling for the pediatric development program of rivaroxaban.
  1. PBPK-based body-weight-adjusted dose was tested in the first-in-children study ('learning' step)
  2. PK data were compared with the model predictions to allow for PBPK model refinement
  3. PopPK for post hoc comparison with the PBPK predictions ('confirmation' step).
  4. Predict / optimize various dosing regimens for phase II and III studies ('prediction' step).



Willmann S et al. Thromb J. 2018 Dec 4;16:32. doi: 10.1186/s12959-018-0185-1.

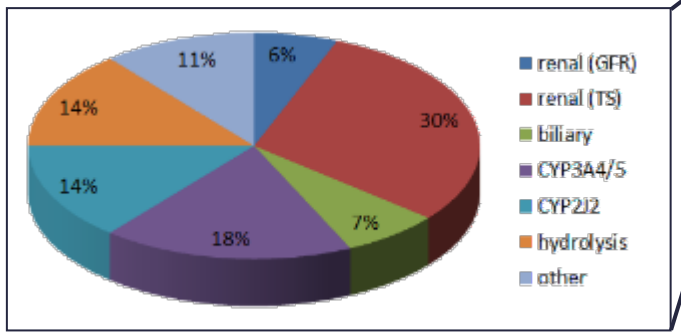
Paediatric PBPK | Case example Rivaroxaban

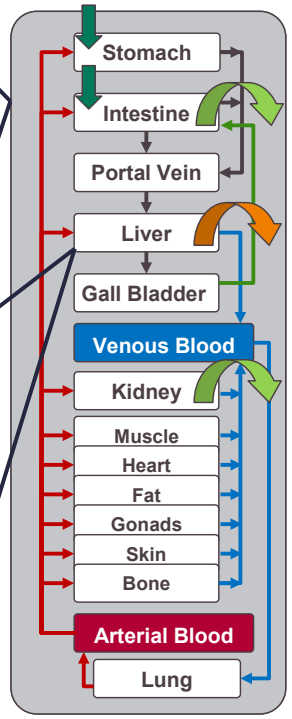
Workflow for scaling PK using PBPK

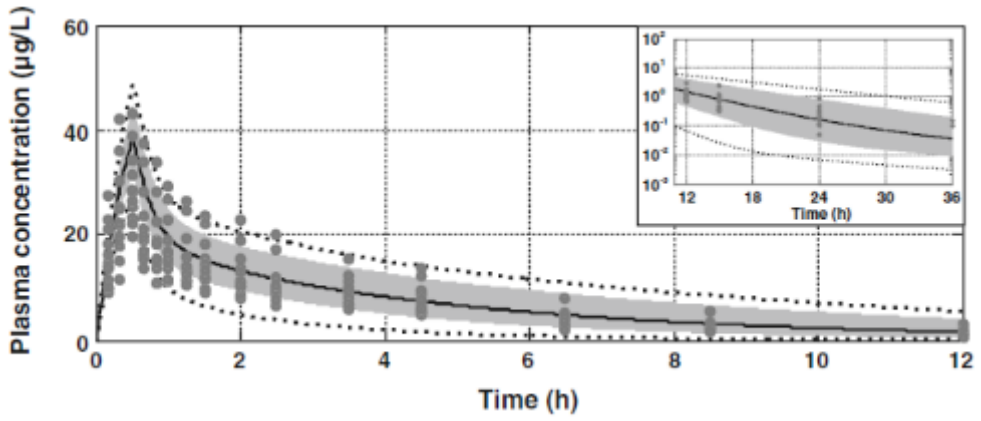
- Step 1: Development and validation of a Rivaroxaban PBPK Model for Adults

Development using physico-chemical data, preclinical and clinical IV/PO data:

Lipophilicity	2.275
Plasma Protein Binding	5.1%
Solubility	
solubility in FaSSIF	20 mg/L
solubility in FeSSIF	80 mg/L
Molecular Weight	435.89 g/mol
Intestinal Permeability	
in the small intestine	4.74 x 10^{-6} cm/s
in the large intestine	9.48 x 10^{-6} cm/s







Willmann et al., Clin. Pharmacokin. (*2013*)

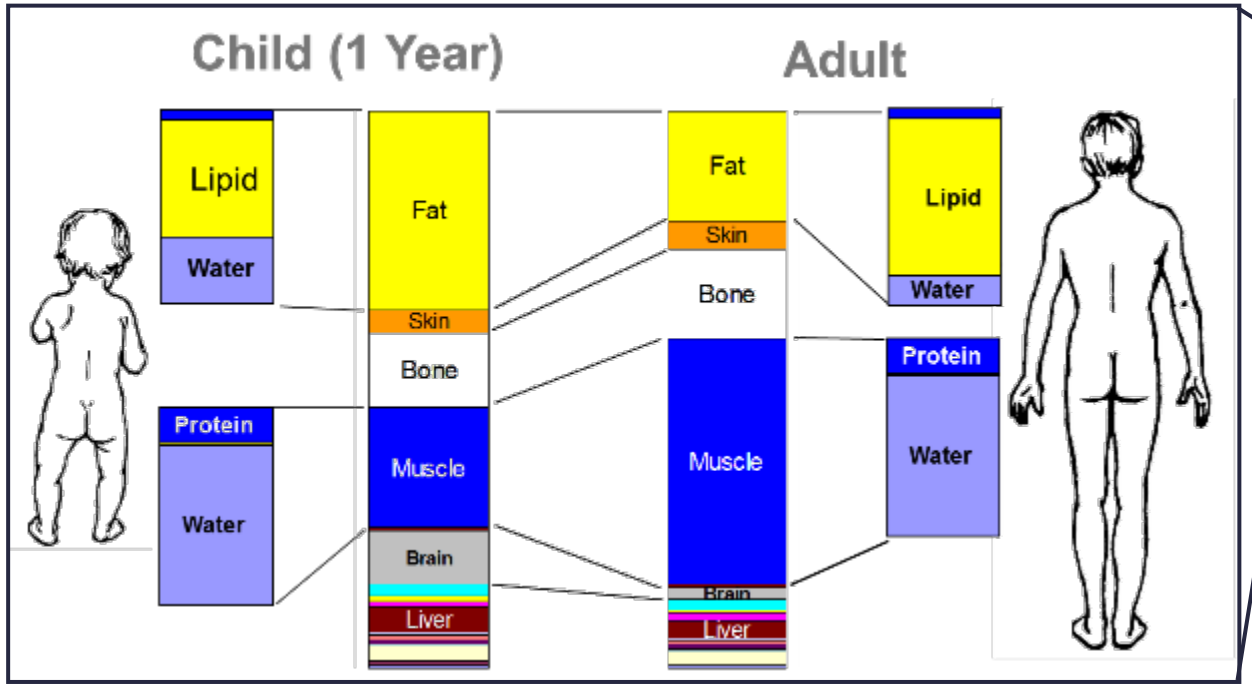
Willmann S et al. Thromb J. 2018 Dec 4;16:32. doi: 10.1186/s12959-018-0185-1.

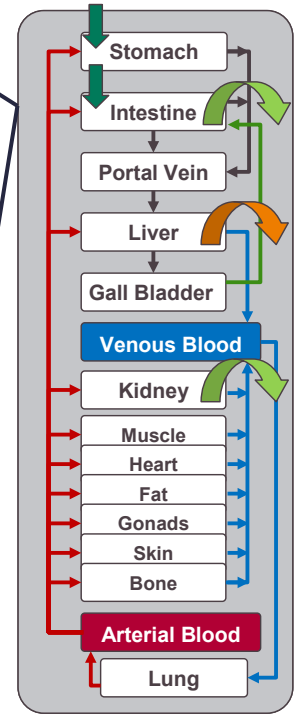
Paediatric PBPK | Case example Rivaroxaban

Workflow for scaling PK using PBPK

- Step 2: 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



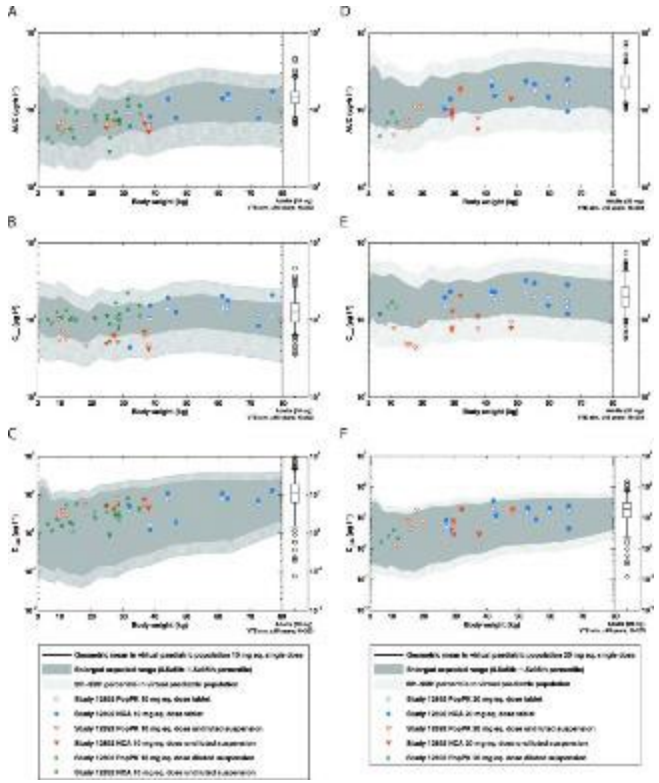


Willmann et al., Clin. Pharmacokin. (*2013*)

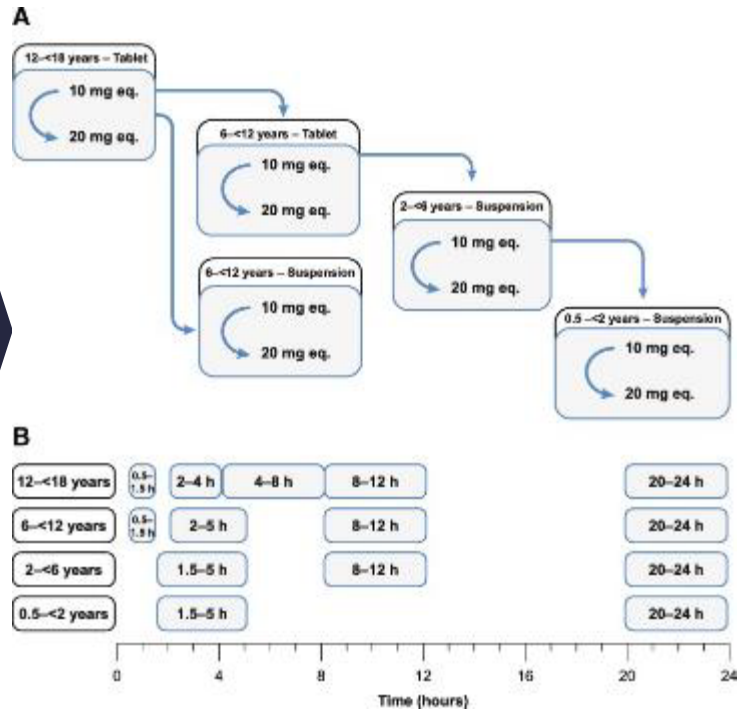
Paediatric PBPK | Case example Rivaroxaban

Workflow for scaling PK using PBPK

- Step 3: Prediction of Rivaroxaban pharmacokinetics in pediatric populations



Result: Age and body weight adapted dosing



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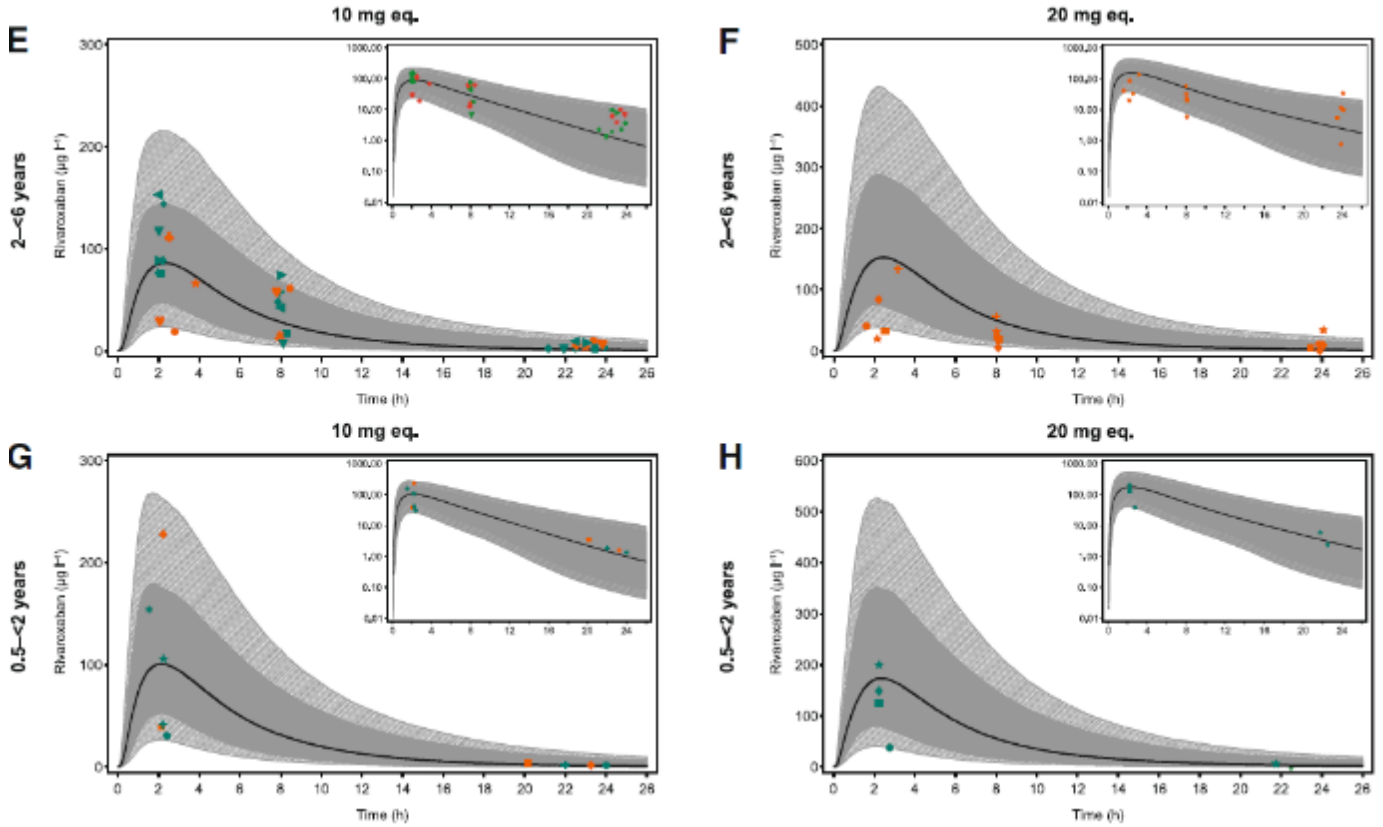
Paediatric PBPK | Case example Rivaroxaban

Workflow for scaling PK using PBPK

- Step 3&4: Confirmation (of predictions) of the Rivaroxaban PBPK model for children



Willmann S et al. Thromb J. 2018 Dec 4;16:32. doi: 10.1186/s12959-018-0185-1.

06

Summary & Outlook

OSP and Pediatrics Formulation Development

Where are we headed?

OSP Vision & Mission

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.

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.

ESQ in **ESQ**labs

Adding Value in the R&D value chain

Efficacy

Safety

Quality

Thank You

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