Modeling and Simulation using Pediatric Ontogeny Information

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FDA/MCERSI Pediatric Ontogeny Workshop

Natcher Conference Center, Bethesda, MD

PBPK modeling in adults and translation to children

Building blocks of a PBPK model for adults

Drug properties

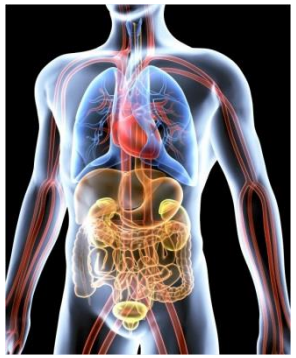
Physicochemical properties

- Lipophilicity
- Molecular weight
- pKa/pKb

Drug-biology interaction

- Fraction unbound
- Partition coefficients
- Mass Balance
- Fractional CL contributions
- Permeability
- Active processes (K_m, V_{max})

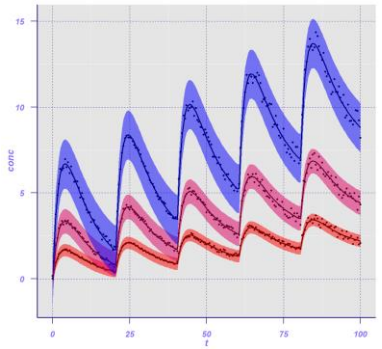
Organism properties



Anatomy & physiology

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

Study protocol and formulation properties



Formulation
(empirical or mechanistic dissolution function)

Administration protocol
(dose and dosing regimen)

Special events
(food intake, exercise, EHC)

Building blocks of a PBPK model for children

Drug properties

Physicochemical properties

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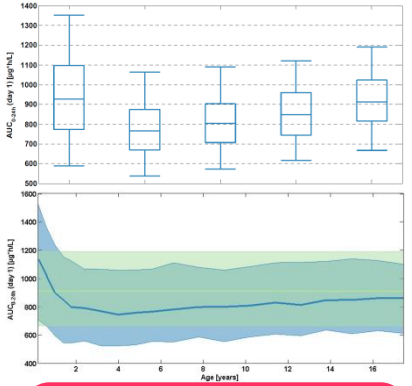
Resulting age-dependent changes in drug-biology interaction

Organism properties

Age-dependent changes in anatomy & physiology

Study protocol and formulation properties



Modified formulations
(e.g. minitablets, syrup)

Adjusted administration protocol
(e.g. mg/kg dosing)

Different special events

Bridging from adults to children - Workflow

Step 1:

Development and verification
of a PBPK model for adults

Step 2:

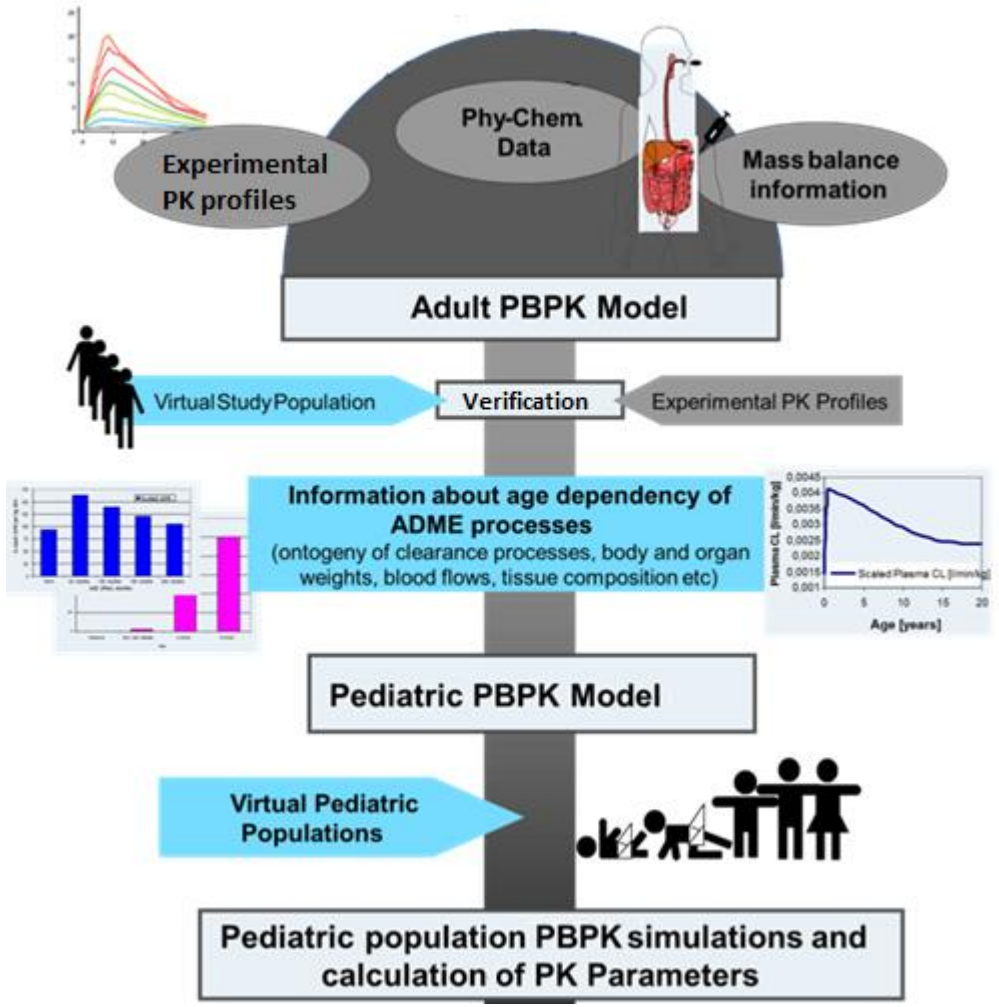
Translation of the adult PBPK model
to children using prior physiological information
about growth and maturation of relevant
processes

Step 3:

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

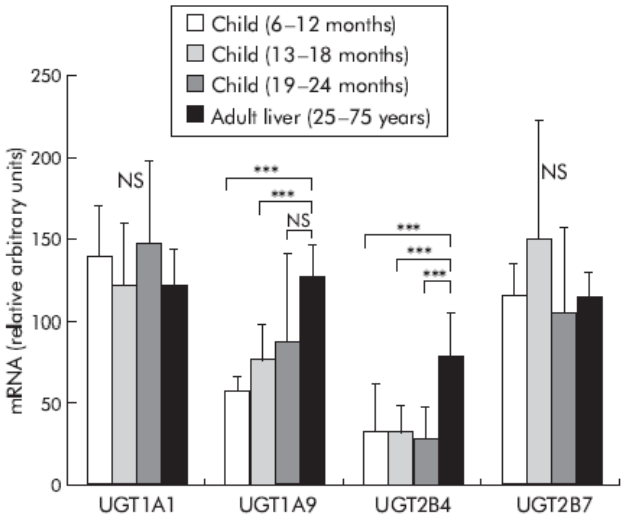
Step 4:

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

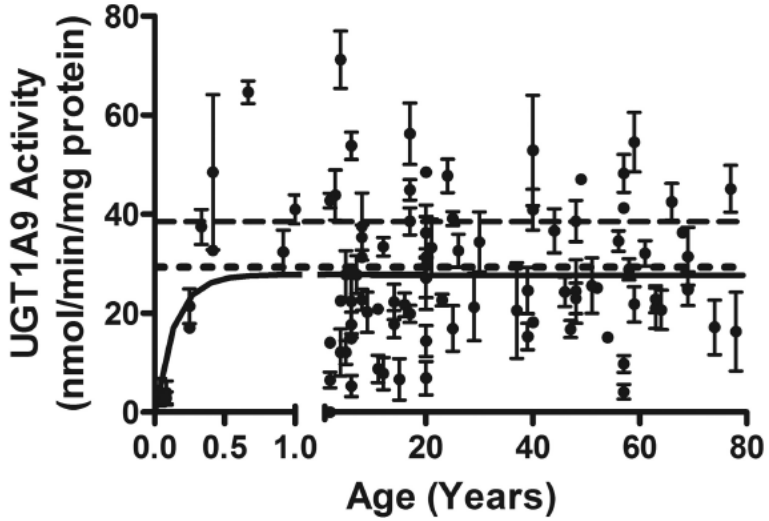


Modified from Edginton et al., Clin. Pharmacokin. (2006)

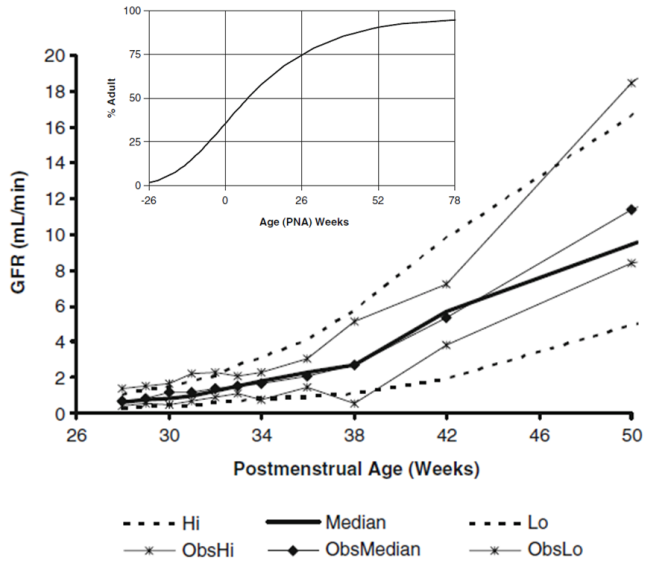
Quantitative ontogeny information is established for many CYPs, some UGTs and GFR



Strassburg, Gut (2002)



Miyagi, drug met. and disp. (2002)



Rhodin, Ped. Nephrology (2008)

Table II. Estimated age-dependent enzyme activity as a fraction of adult values[a]

	Fraction of adult activity				
Age	CYP3A4	CYP1A2	CYP2E1	UGT2B7	UGT1A6
Premature	0.1	0.02	0.1	0.015	0.015
Term	0.2	0.05	0.21	0.05	0.1
7 days	0.24	0.1	0.32	0.064	0.11
1 month	0.5	0.2	0.4	0.1	0.16
3 months	0.7	0.25	0.46	0.3	0.25
6 months	1.1	0.29	0.46	0.7	0.36
1 year	1.3 (1–3y)	0.35	1	1	0.5
10 years	1	1 (8y)	1	1	1

a Values were based on *in vitro* and *in vivo* clearance data gathered from the literature from children of all ages.
CYP = cytochrome P450; **UGT** = uridine diphosphate glucuronosyltransferase.

Edginton et al., Clin. Pharm. (2008)

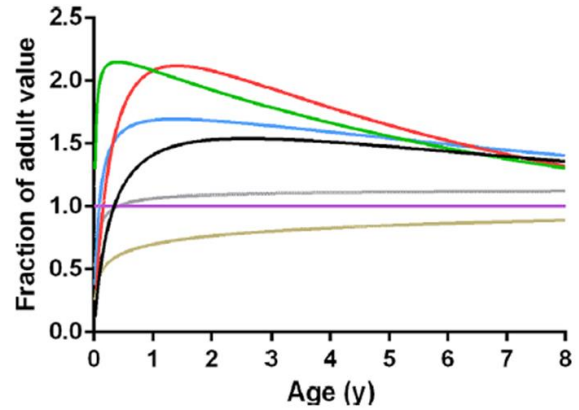
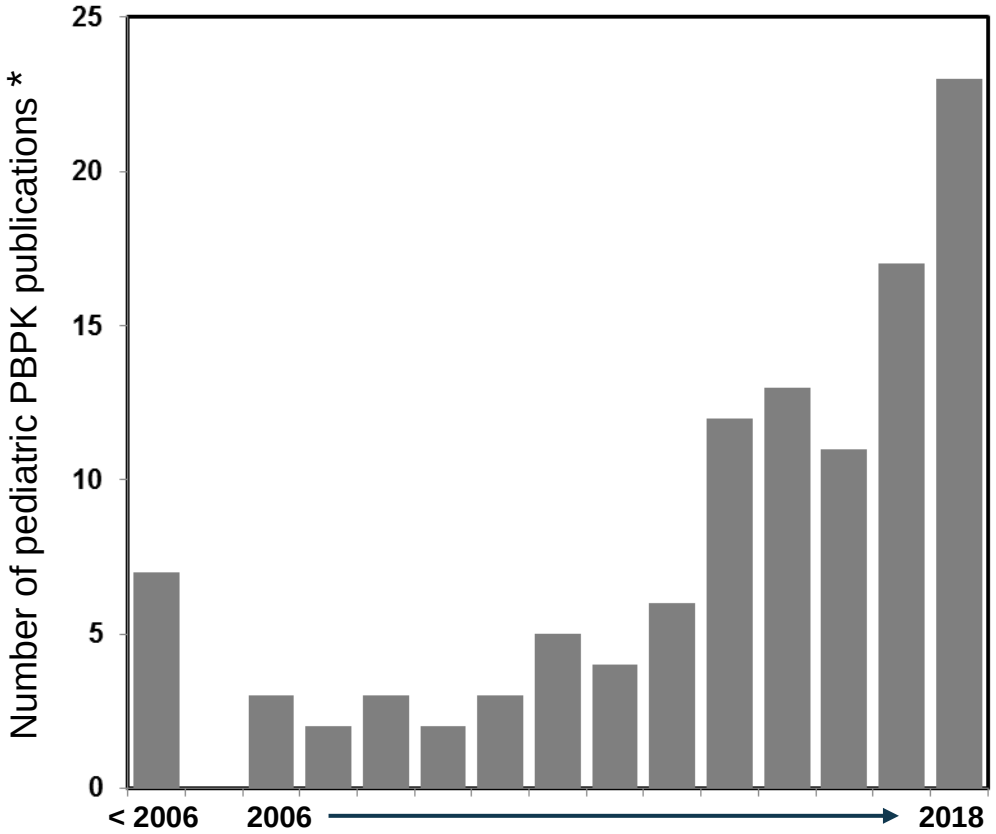


Figure 2. An integrated visualization of in vivo CYP ontogeny for the major hepatic CYPs: (A) CYP1A2 (black), (B) CYP2A6 (gray), (C) CYP2B6, CYP2D6 (purple), (D) CYP2C9 (green), (E) CYP2C19 (red), (F) CYP2E1 (gold), and (G) CYP3A (blue).

Upreti et al, PediatricPharmacology (2016)

Numerous examples of PBPK models for children have been published in recent years



* according to PUBMED-search performed 01/2019 for „PBPK“ AND („children“ OR „pediatric)“, including toxicokinetic/environmental health models, excluding review articles

Concept to use PBPK for the description of PK in children using (among other prior physiological knowledge) ontogeny data is proven

BUT:

- the majority of published articles deal with labelled drug thats are known for quite some time and are partially retrospective
- for these compounds, the required information – in particular mass-balance information and ontogeny data of the relevant elimination processes – is available

➢ for typical drug development candidates, less information is available

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

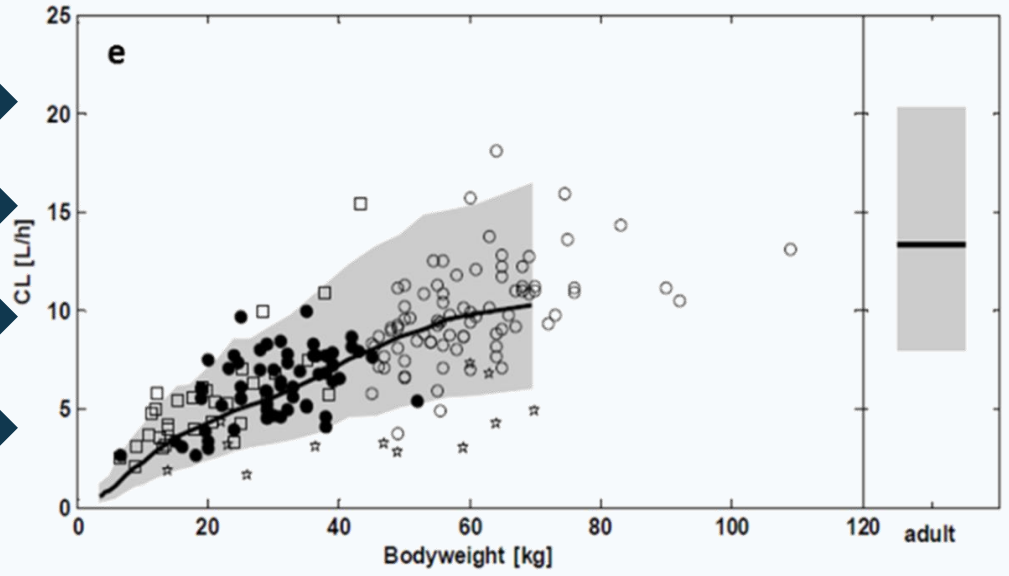
SULT2A1

UGT1A1

biliary

renal

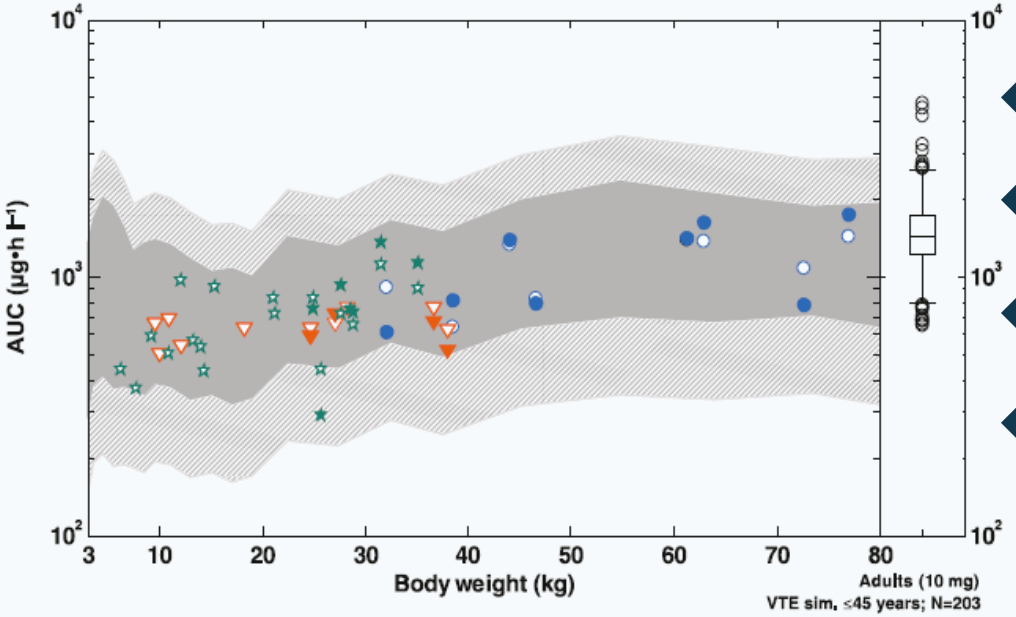
Example: Moxifloxacin



- 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., *submitted for publication*

Example: Rivaroxaban



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

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

CYP3A4

CYP2J2

hydrolysis

renal

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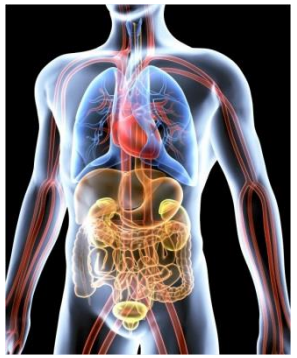

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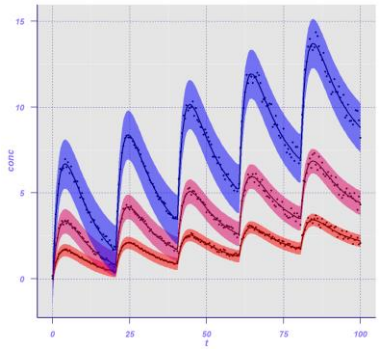

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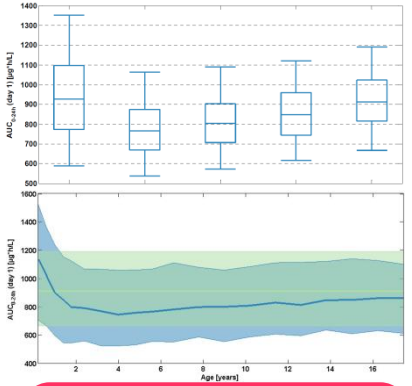

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(e.g. mg/kg dosing)

Different special events

Novel drug modalities pose new challenges to pediatric drug development

Increasing number of “non-classical small molecules” are developed including large proteins (e. g. antibodies), antisense-oligonucleotides, small interfering RNA, vector-based gene therapies, ……

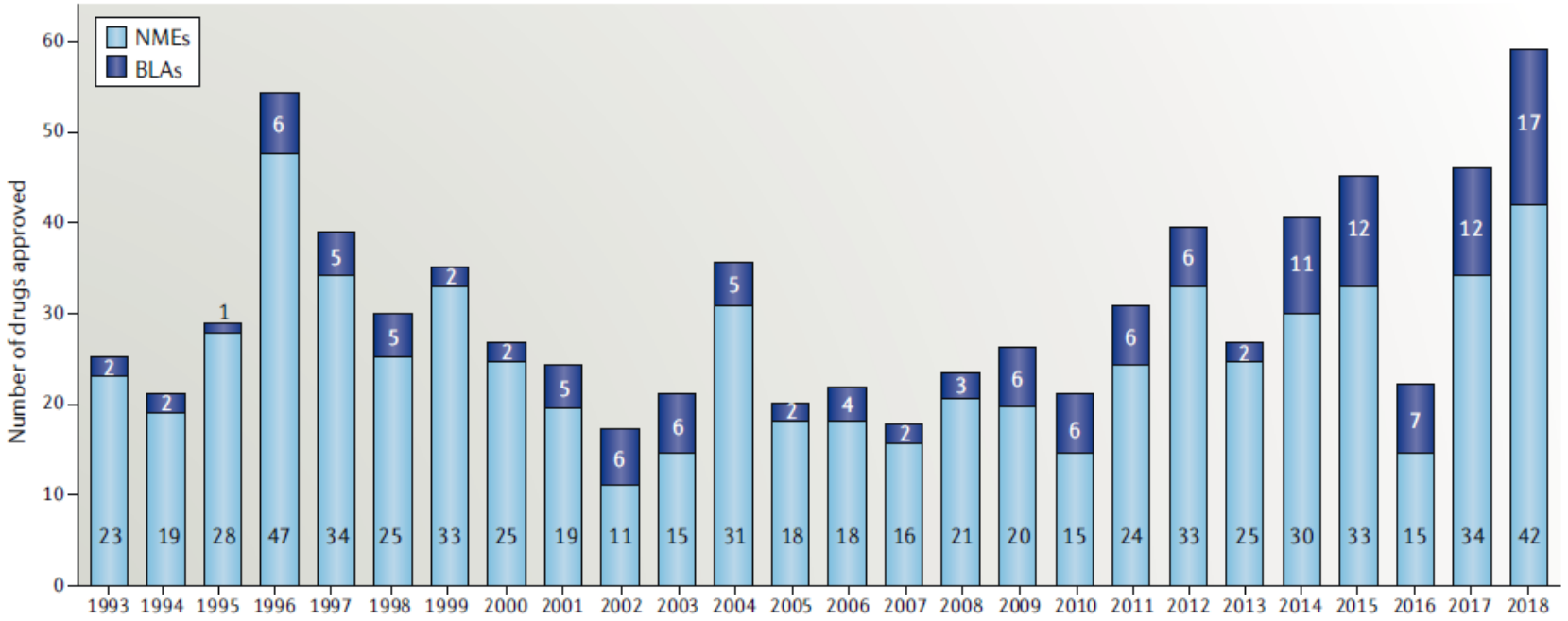


Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2018. Approvals of products such as vaccines by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count (see Table 2). Source: Drugs@FDA.

Source:Nature Reviews Drug Discovery Vol. 18, February 2019

Physiologically-based PK/PD modelling of therapeutic proteins

Mechanisms/processes relevant for therapeutic proteins

- subcutaneous or intramuscular absorption
- extravasation and lymph flow
- target mediated disposition
- lysosomal proteolysis and recycling by FcRn
- immunogenicity

AGE ?

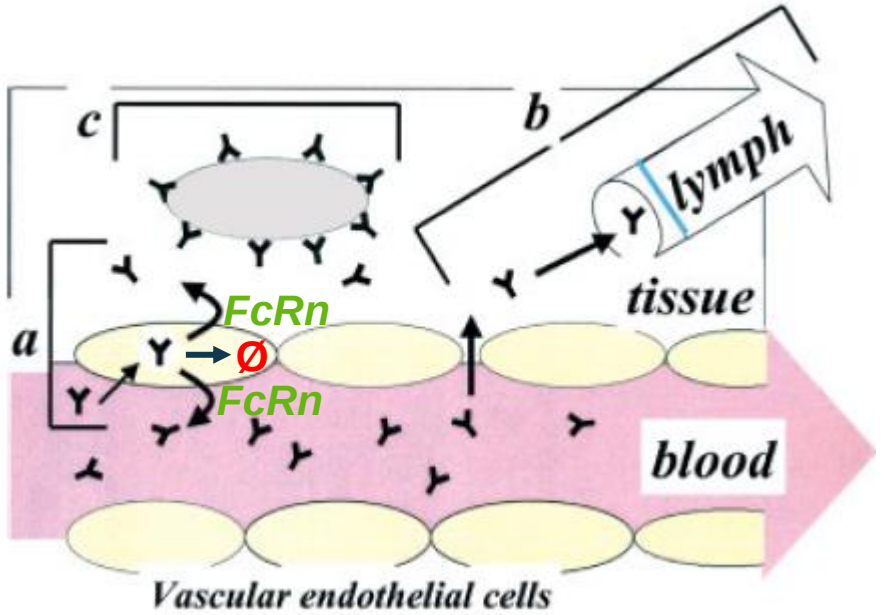


Figure adapted from Lobo *et al*. (2004). *J. Pharm. Sci*, *93*(11), 2645

Maturation information for relevant processes is sparse

- although age-dependence of many relevant physiological parameters and processes have been reviewed recently*, it is currently difficult to fully define *a-priori* an age-dependent parameterization of PBPK models for therapeutic proteins.
- assessment of performance of a generic antibody PBPK model performance is currently ongoing

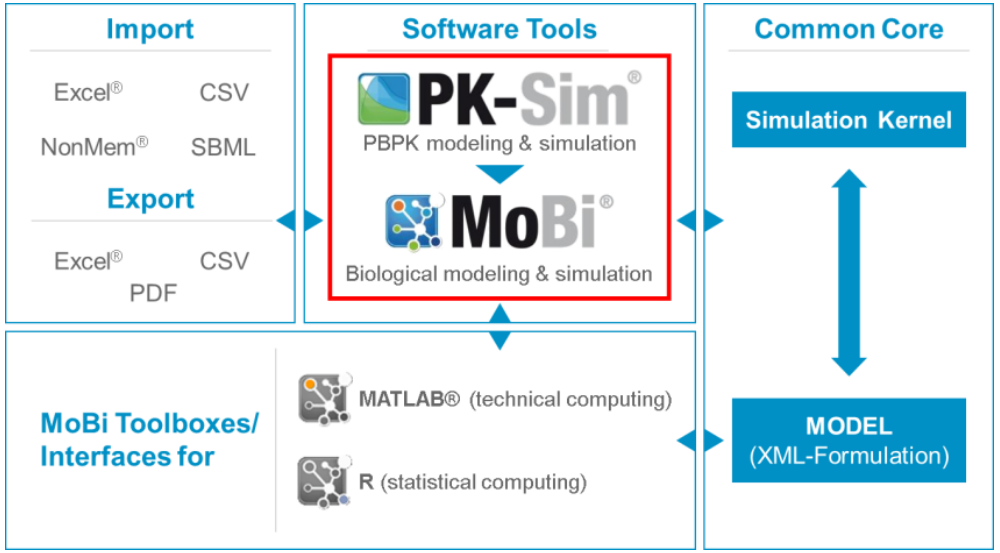
* Malik & Edginton, *Expert Opin. Drug Metab. Toxicol.*, *14*, 585-599 (2018)

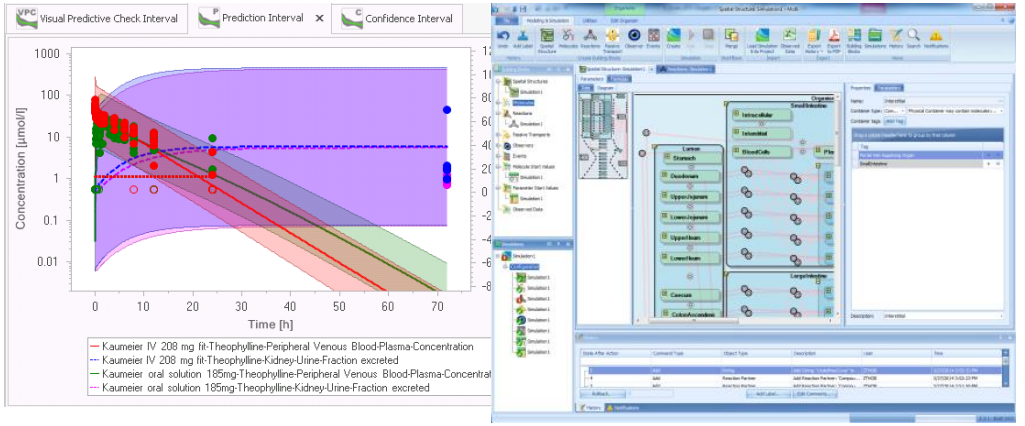
Open-Systems-Pharmacology.org

Open Systems Pharmacology Suite

PK-Sim®, MoBi® & toolboxes now open source freeware under GNU Public License v2.0

- **Fully transparent open source development**
- **Open development of scientific content and qualification approaches**
- **Repositories for open PBPK and Systems Pharmacology models**





Pediatric Ontogeny Qualification

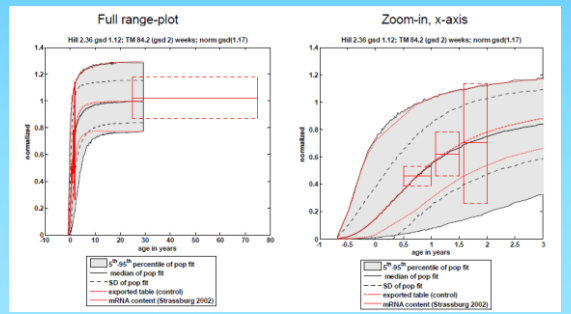
Qualification and publication of PK-Sim® Ontogeny database

// To qualify OSP software content, *in vivo* probe substances are applied to continuously evaluate predictive performance

PK-Sim® Ontogeny Database

In vitro / in vivo based functions

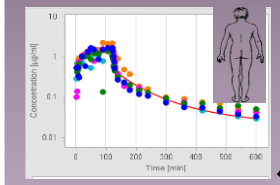
E.g. UGT1A9



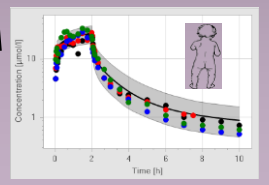
Qualification

In vivo predictions

E.g. Propofol



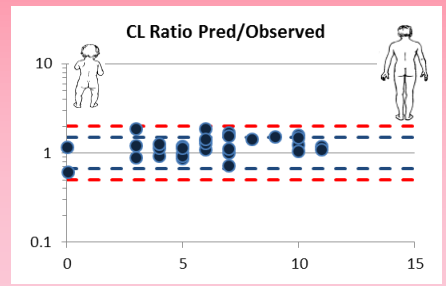
Build
Adult PBPK model



Predict
Pediatric PK

Publish Results

1. **Adult model performance**
2. **Pediatric translation**
3. **Predicted vs Reported Ratio plots**



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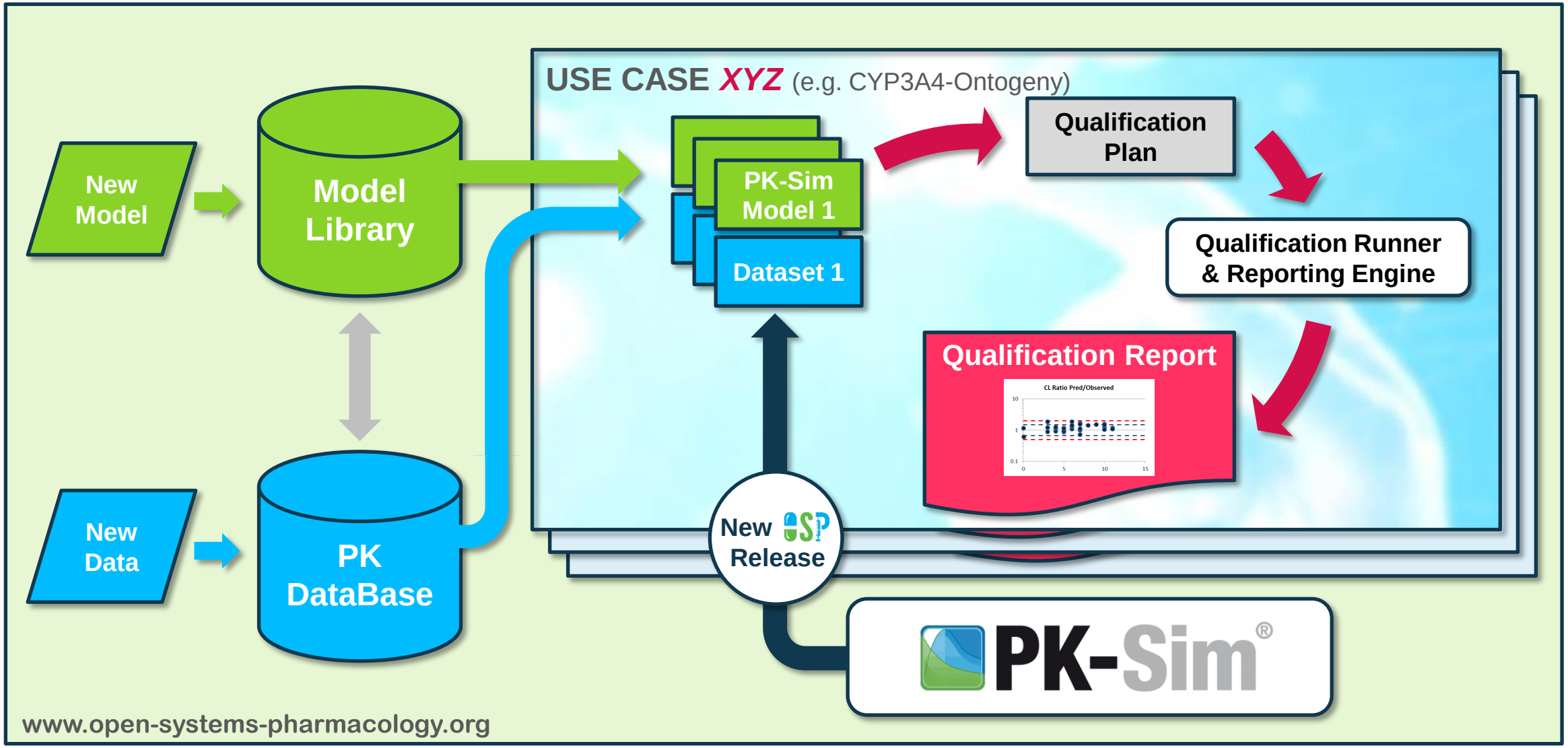
OSP Automatic (Re)-Qualification Workflow



OSP Automatic (Re)-Qualification Workflow

Pediatric Ontogeny Qualification

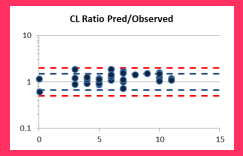
Contents

(e.g. CYP3A4-Ontogeny)

Qualification Plan

Qualification Runner & Reporting Engine

Qualification Report



PK-Sim®

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OSP Automatic (Re)-Qualification Workflow

1. Open Systems Pharmacology Suite (OSPS)

OSPS is a tool for PBPK modelling and simulation of drugs in laboratory animals and humans. PK-Sim and MoBi are part of the Open Systems Pharmacology Suite (OSPS) [1]. Simulations were carried out on a validated computerized system. PK-Sim® is based on a generic PBPK-model with 18 organs and tissues. Represented organs/tissues include arterial and venous blood, adipose tissue (separable adipose, excluding yellow marrow), brain, lung, bone (including yellow marrow), gonads, heart, kidneys, large intestine, liver, muscle, portal vein, pancreas, skin, small intestine, spleen and stomach, as shown in Figure 1.

Each organ consists of four sub-compartments namely the plasma, red blood cells (which together build the vascular space), interstitial space, and cellular space. Distribution between the plasma and red blood cells as well as between the interstitial and cellular compartments can be permeability-limited. In the brain, the permeation barrier is located between the vascular and the interstitial space. PK-Sim® estimates model parameters (intestinal permeability [2], organ partition coefficients [3,4], and permeabilities) from physico-chemical properties of compounds (molecular weight, pKa, ace/base properties) and the composition of each tissue compartment (lipids, water and proteins). Partition coefficients can be calculated using a variety of methods available in PK-Sim®, for example the internal PK-Sim® method [3,4] or that of Rodgers and Rowland [5-7].

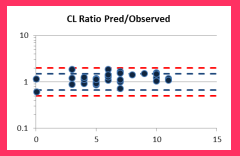
Physiological databases included in the software incorporate the dependencies of organ weights, organ blood flows and gastrointestinal parameters (gastrointestinal length, radius of each section, intestinal surface area [[2]) with the user-defined body weight and height of the individual [8]. Thereby, PK Sim® allows generating realistic virtual populations. For a detailed description of the PBPK model structure implemented in PK Sim®, see Willmann et al. [2,4,8,9] or the Open Systems Pharmacology (OSP) Suite homepage (https://github.com/Open-Systems-Pharmacology).

(e.g. CYP3A4-Ontogeny)

Qualification Plan

Qualification Runner & Reporting Engine

Qualification Report



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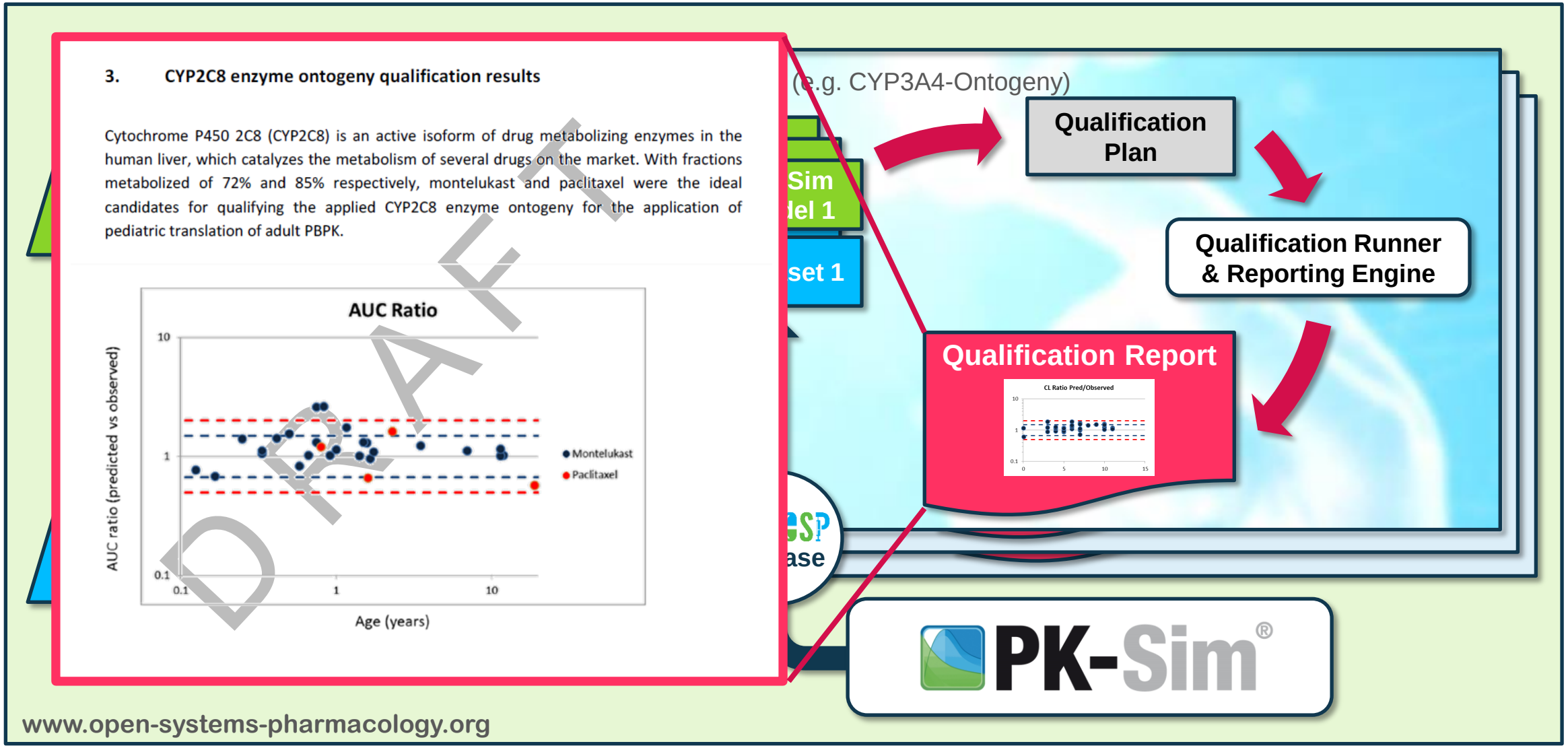

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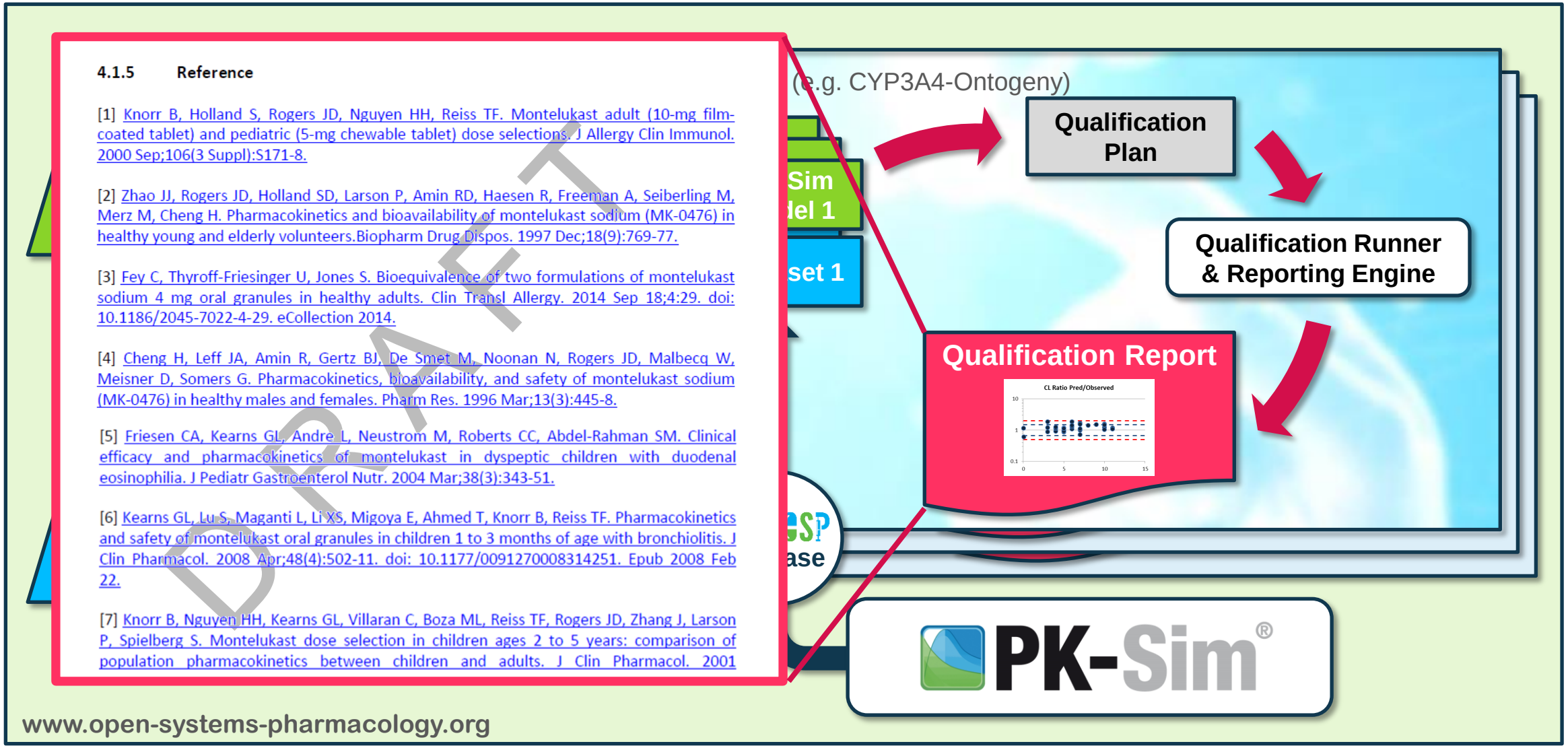

Summary and Conclusions

- **Present state of knowledge of ontogeny**
  - ✓ Numerous papers have been published containing ontogeny information (-> detailed discussion in the following session)
  - ✓ Workflows and processes for automated qualification of software content - including pediatric ontogeny functions - are under development (publishing in June 2019)
- **Adequacy of knowledge of ontogeny of specific systems**
  - ✓ For many processes relevant for **small molecules** sufficient ontogeny data and information is available and integrated into PBPK modelling platforms
  - ? For processes relevant for **novel (biologic) drug modalities** ontogeny information is widely lacking

Thank you!

Ibrahim Ince
Sebastian Frechen
André Dallmann
Christoph Niederalt
Juri Solodenko
Kristin Menke
Jan Schlender
Rolf Burghaus
Jörg Lippert