Science For A Better Life

Qualification of PBPK platform – experience with PK-Sim

2016-11-21 Michael Block

EMA workshop on qualification and reporting of PBPK modelling and simulation

Questions

- How would you qualify a PBPK platform for an intended purpose, as outlined in the Guideline?
- How would you qualify the next version of the PBPK platform for the same use ?
- Do you agree with the qualification dataset descriptions as outlined in the guideline?
- Are the approach of the 3 practical qualification processes adequate?
- In a constructive way - what changes would you propose?

Application & qualification

Current use of PBPK

- PBPK platform **integrates pharmacology relevant knowledge, assumptions and data** including drug related and additional prior knowledge
- Revealing inconsistencies between different sources of information enables to **identify risks**
- By consequent integration along the R&D process it allows **prediction of most likely outcomes of future experiments and enables decision making** and optimization of development strategies and study designs at the current best state of knowledge

Qualification for an application requires different steps

System qualification – technical qualification of the software

- An **agile software development process.**
  Release candidate which is tested in a formalized and documented process meeting GAMP 5 guidelines and complying with ISO9001 and FDA 21 CFR Part 11.
- **Change management:** Change requests documentation in a tracking system.
- **Version control**: Software development history is automatically documented with a versioning system (SVN).
- **Validation of computerized system:** Comprehensive **library of test cases** that grows with every newly released feature, including manual or automatic with validated programs.

Technical qualification of the software

System qualification – technical qualification of the software

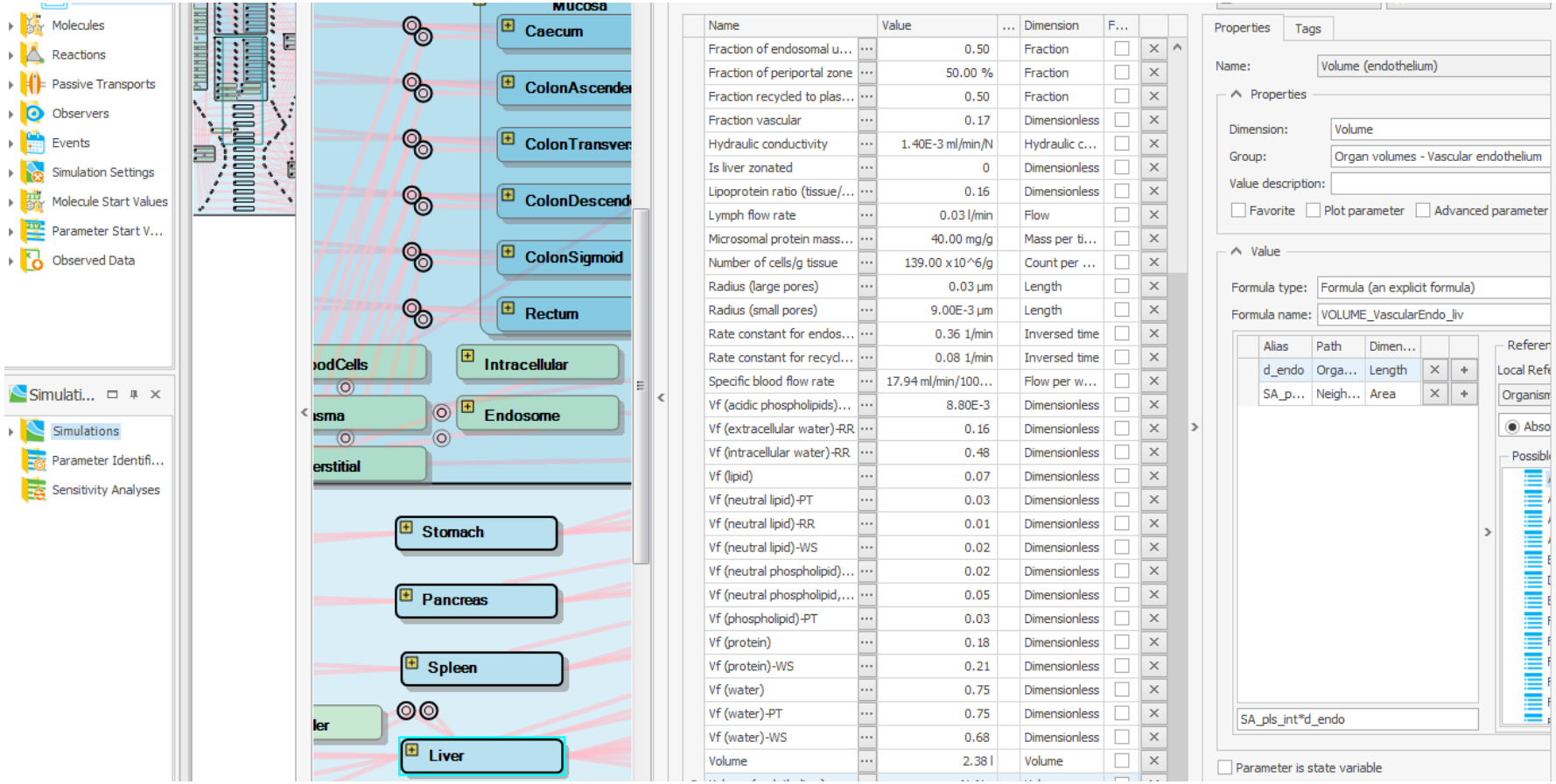
Testing correct behavior of software modules. Tests triggered with every software build (every day) (Unit Tests, Integration Tests).

Comparison of simulation outputs to verified standards for specific combinations of compounds, organisms, calculation methods, and model options.

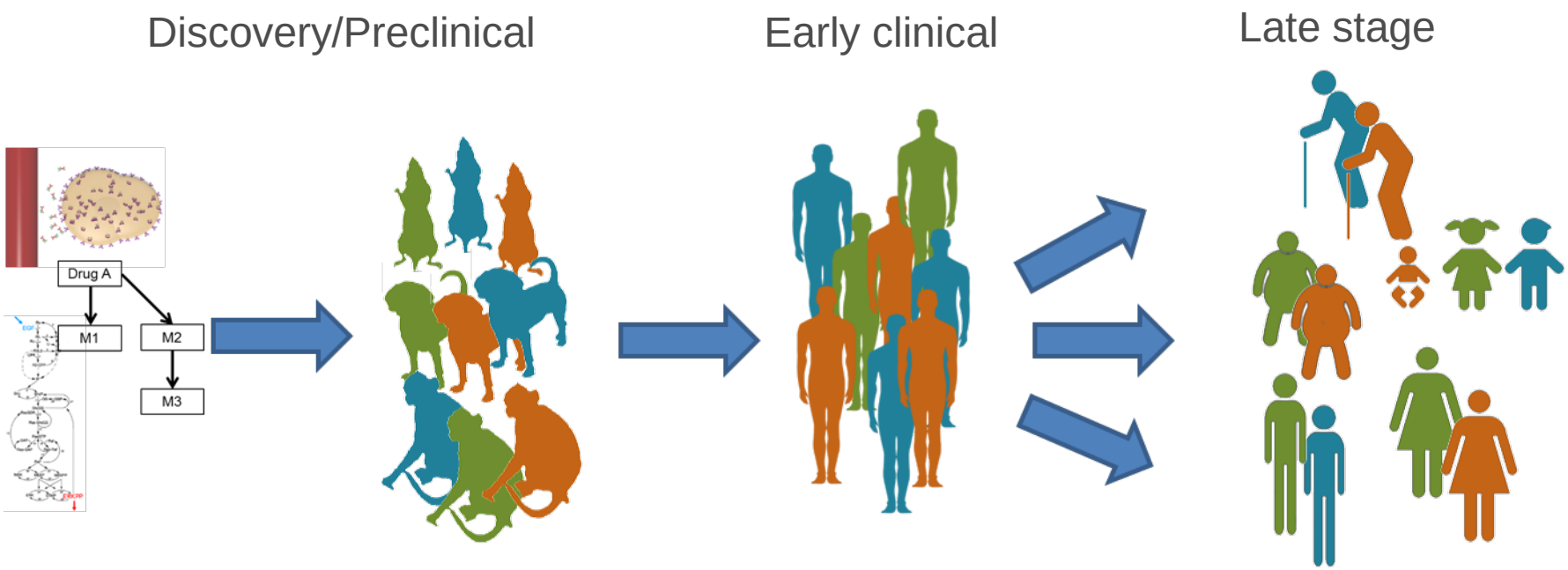
environments.

System qualification – technical qualification of the software

Full transparency of model structure, equations, and parameterization

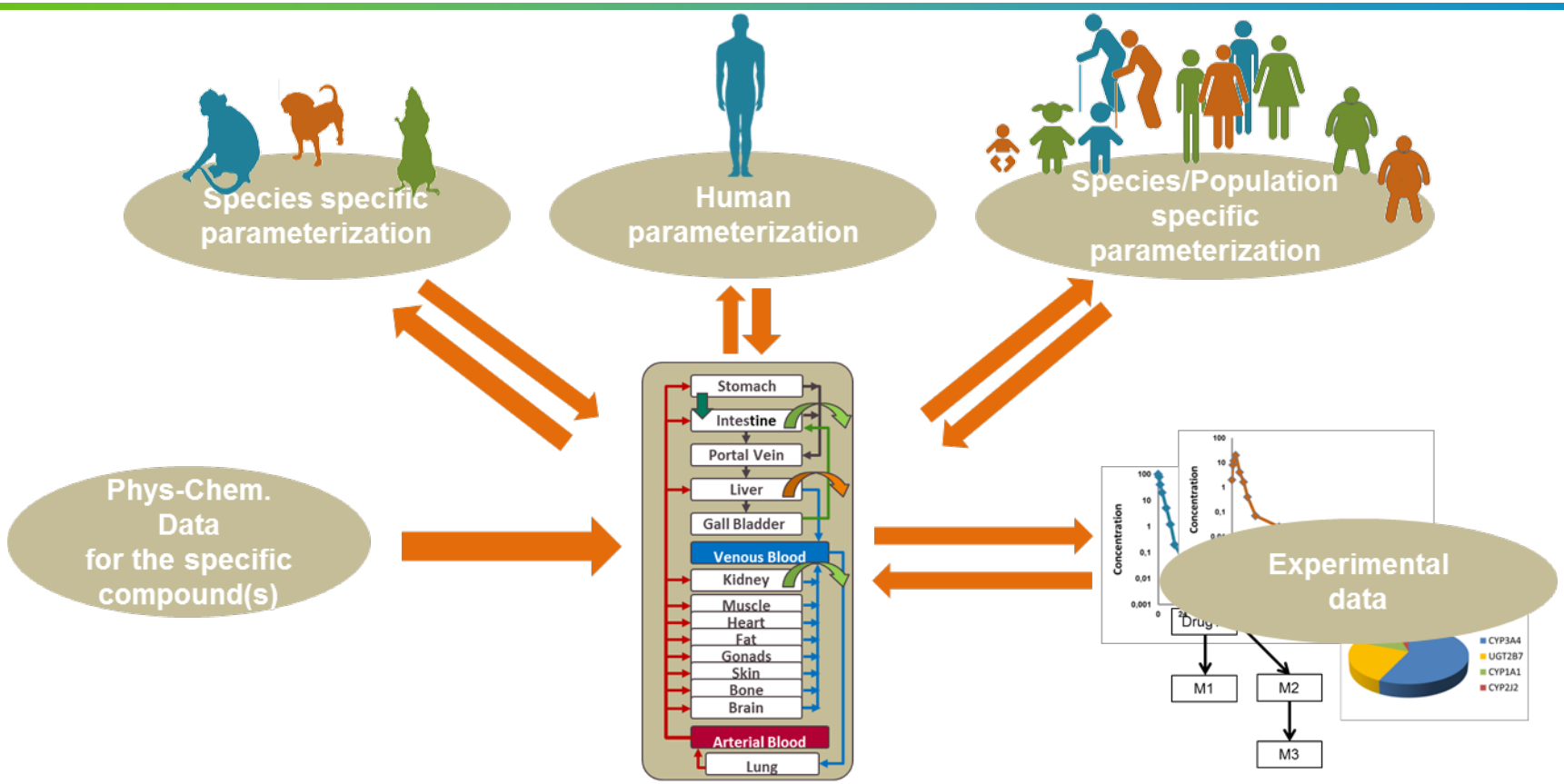


Workflow in development



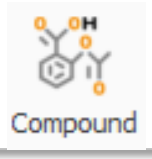
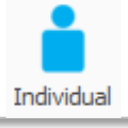
Workflow for model development of the PBPK has to cover the development process to account for the level of knowledge at the different steps

Workflow for PBPK application



Workflow follows development process
Qualification requires modular concept for the different model components

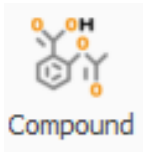
Modular concept

 Compound	Physicochemical properties (lipophilicity, molecular weight, pKa) Drug biological properties (small/large, fu, partion coefficients, permeability, active processes)
 Individual	Enzymes, transporter, … mouse, rat, beagle, monkey, human, …
 Population	ICRP, NHANES, Tanaka, … Healthy, renally impaired, ChildPughA/B/C, other diseased populations Adults, children, preterm, elderly Geno/Phenotype (PM, EM, IM),…
 Administration Protocol	Type: IV, PO, … QD, BID, Q3W,… mg, mg/kg, mg/m^2…
 Formulation	Dissolved, particle dissolution, empirical functions
 Event	Food intake, different meal types, exercise, …

Why a modular concept?

use of prior knowledge by development with modules

Developed PBPK model



Small molecule
…

Dissolved

4 weeks
BID
po

ICRP
healthy
adult

ICRP
healthy
children

Different applications are often just exchange of one module, where all other modules are still at the same stage of qualification

General qualification of the PBPK platform

Qualification of the structure

- Qualified by design
  - Based on biological structure (physiologically based) and relevant biological processes (absorption, distribution, metabolism, excretion)
  - Only slight structural changes between species (human, monkey, dog, rat, mouse, cattle, cat, rabbit)

Qualification of physiological parameters

- Some of them qualified by design
  - E.g. input from studies (weight, height,…)
- Others qualified by prior information
  - Literatue values, different project experience, learning…

Qualification of proteins, enzyme, transporter parameters

- From experiments, taken as a priori information
- Inferred parameters from estimation based on data

Examples for the use of PBPK

Utilizing *In Vitro* and PBPK Tools to Link ADME Characteristics to Plasma Profiles: Case Example Nifedipine Immediate Release Formulation

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Even if there are a lot of approaches with PBPK available and accepted in the scientific community, the level of integrated knowledge differs

Answers to questions

Do you agree with the qualification dataset descriptions as outlined in the guideline?

- Current description could be more specific

Answers to questions

Are the approach of the 3 practical qualification processes adequate?

- CHMP qualification
  - Provides a clear transparent view on qualified platforms/applications
  - Reduces efforts for applicant
  - Not very clear, how a comprehensive qualification should look like
  - What is required, if parts(modules) of the PBPK model development are already parts of a qualified application?
- Single qualification in the application
  - Provides a qualification if no CHMP qualification is in place
  - Multiplies efforts, if qualification do not lead to overall qualification
- Learning societies
  - Possibly simplifies qualification for providers, applicants, and agencies
  - Not very clear from the guidance what “qualification by a learning society” means in detail

Answers to questions

In a constructive way - what changes would you propose?

- From a modelers view and possibly for learning societies as well as for regulators, transparency of modeling and models would increase the quality of applications
- Consider transparency of modeling and models as a qualifying element

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Thank you!