



Science For A Better Life



Qualification of PBPK platform – experience with PK-Sim

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.

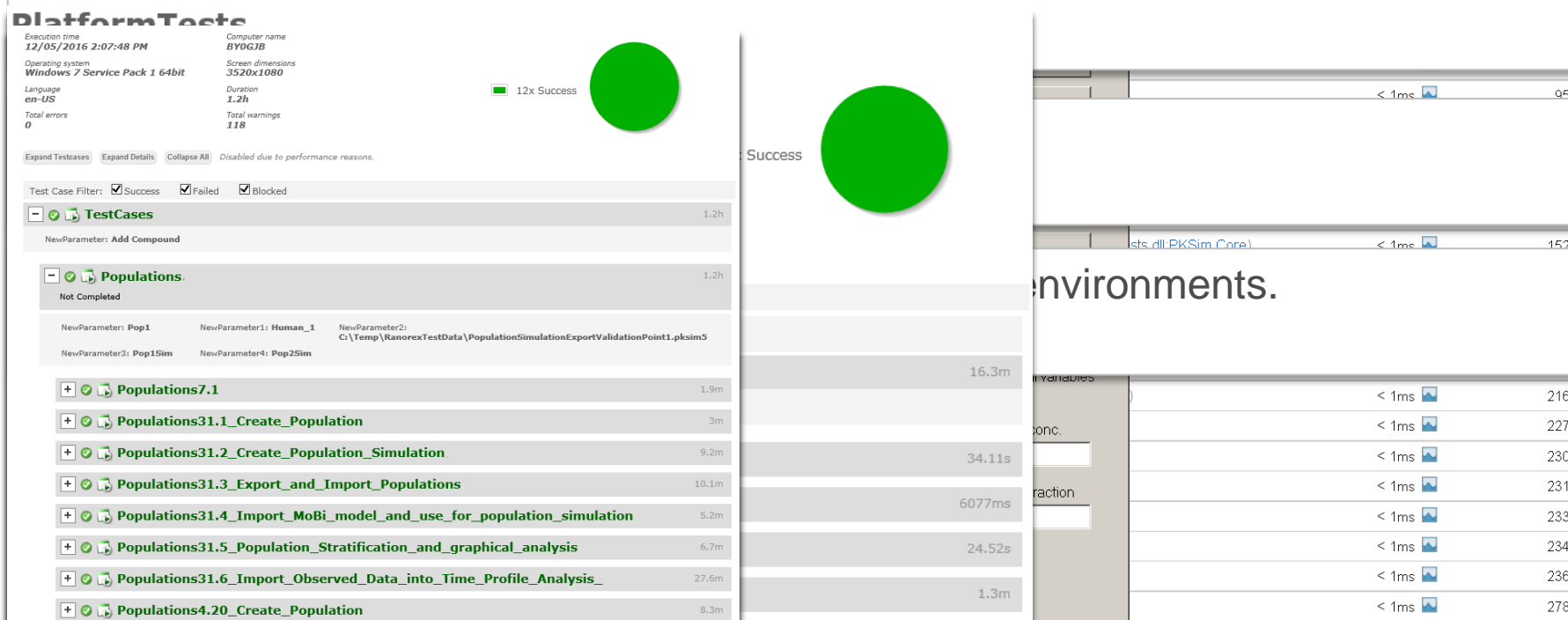


Technical qualification of the software

System qualification – technical qualification of the software

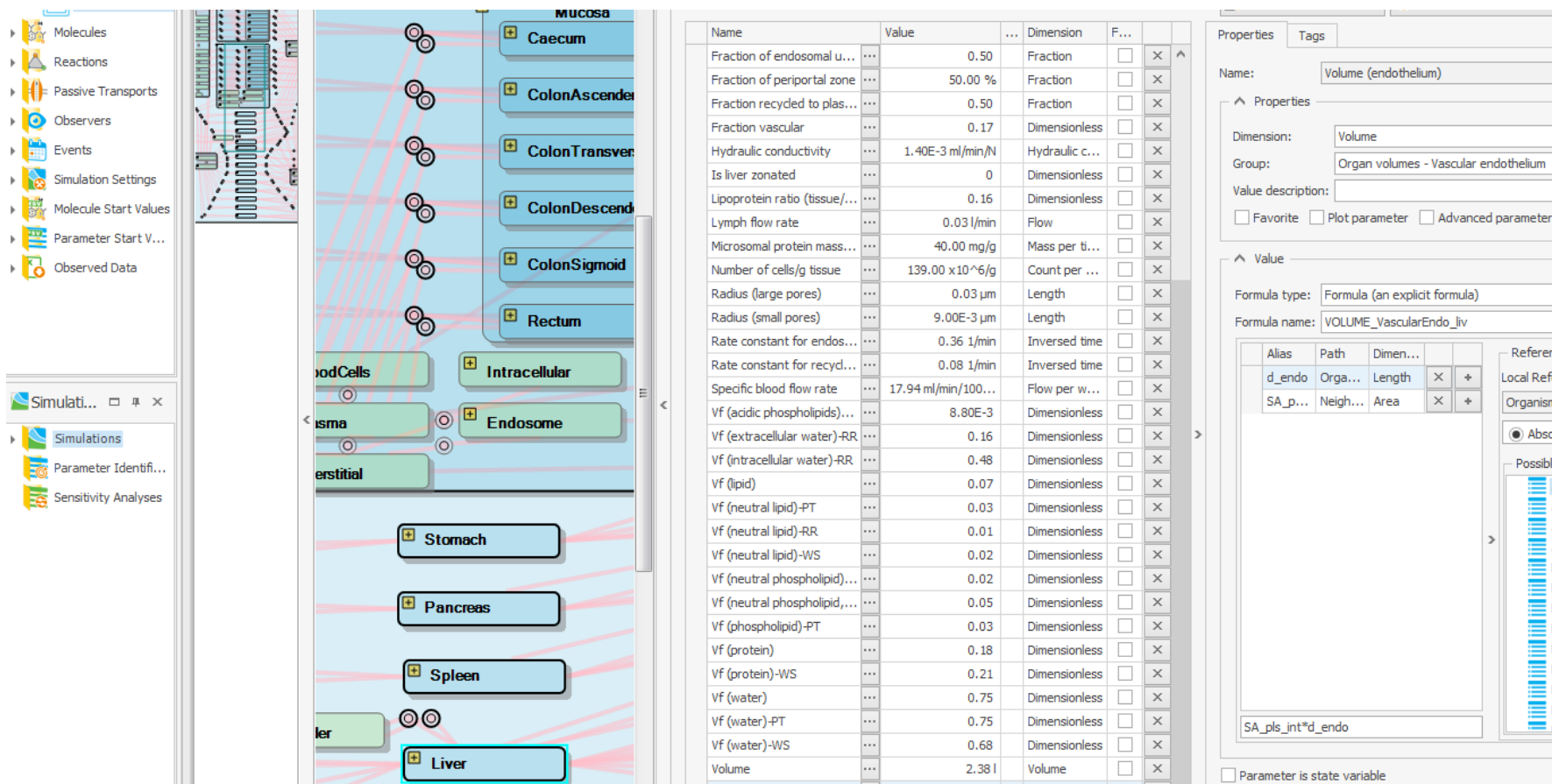
Testing correct behavior of software modules. Tests triggered with every software build (every day) (Unit Tests, Integration Tests).

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



System qualification – technical qualification of the software

Full transparency of model structure, equations, and parameterization



The screenshot displays the software interface for system qualification, showing a hierarchical model structure, a table of parameters, and a properties panel.

Model Structure (Left Panel):

- Mucosa:**
 - Caecum
 - ColonAscendens
 - ColonTransversus
 - ColonDescendens
 - ColonSigmoid
 - Rectum
- FoodCells**
- Intracellular**
- Endosome**
- Extracellular**
- Stomach**
- Pancreas**
- Spleen**
- Liver**

Parameter Table (Middle Panel):

Name	Value	Dimension	F...
Fraction of endosomal u...	0.50	Fraction	<input type="checkbox"/>
Fraction of periportal zone	50.00 %	Fraction	<input type="checkbox"/>
Fraction recycled to plas...	0.50	Fraction	<input type="checkbox"/>
Fraction vascular	0.17	Dimensionless	<input type="checkbox"/>
Hydraulic conductivity	1.40E-3 ml/min/N	Hydraulic c...	<input type="checkbox"/>
Is liver zoned	0	Dimensionless	<input type="checkbox"/>
Lipoprotein ratio (tissue/...	0.16	Dimensionless	<input type="checkbox"/>
Lymph flow rate	0.03 l/min	Flow	<input type="checkbox"/>
Microsomal protein mass...	40.00 mg/g	Mass per ti...	<input type="checkbox"/>
Number of cells/g tissue	139.00 x 10 ⁶ /g	Count per ...	<input type="checkbox"/>
Radius (large pores)	0.03 µm	Length	<input type="checkbox"/>
Radius (small pores)	9.00E-3 µm	Length	<input type="checkbox"/>
Rate constant for endos...	0.36 1/min	Inversed time	<input type="checkbox"/>
Rate constant for recydl...	0.08 1/min	Inversed time	<input type="checkbox"/>
Specific blood flow rate	17.94 ml/min/100...	Flow per w...	<input type="checkbox"/>
Vf (acidic phospholipids)...	8.80E-3	Dimensionless	<input type="checkbox"/>
Vf (extracellular water)-RR	0.16	Dimensionless	<input type="checkbox"/>
Vf (intracellular water)-RR	0.48	Dimensionless	<input type="checkbox"/>
Vf (lipid)	0.07	Dimensionless	<input type="checkbox"/>
Vf (neutral lipid)-PT	0.03	Dimensionless	<input type="checkbox"/>
Vf (neutral lipid)-RR	0.01	Dimensionless	<input type="checkbox"/>
Vf (neutral lipid)-WS	0.02	Dimensionless	<input type="checkbox"/>
Vf (neutral phospholipid)...	0.02	Dimensionless	<input type="checkbox"/>
Vf (neutral phospholipid)...	0.05	Dimensionless	<input type="checkbox"/>
Vf (phospholipid)-PT	0.03	Dimensionless	<input type="checkbox"/>
Vf (protein)	0.18	Dimensionless	<input type="checkbox"/>
Vf (protein)-WS	0.21	Dimensionless	<input type="checkbox"/>
Vf (water)	0.75	Dimensionless	<input type="checkbox"/>
Vf (water)-PT	0.75	Dimensionless	<input type="checkbox"/>
Vf (water)-WS	0.68	Dimensionless	<input type="checkbox"/>
Volume	2.38 l	Volume	<input type="checkbox"/>

Properties Panel (Right Panel):

Name: Volume (endothelium)

Properties:

- Dimension: Volume
- Group: Organ volumes - Vascular endothelium
- Value description:
- ☐ Favorite ☐ Plot parameter ☐ Advanced parameter

Value:

Formula type: Formula (an explicit formula)

Formula name: VOLUME_VascularEndo_liv

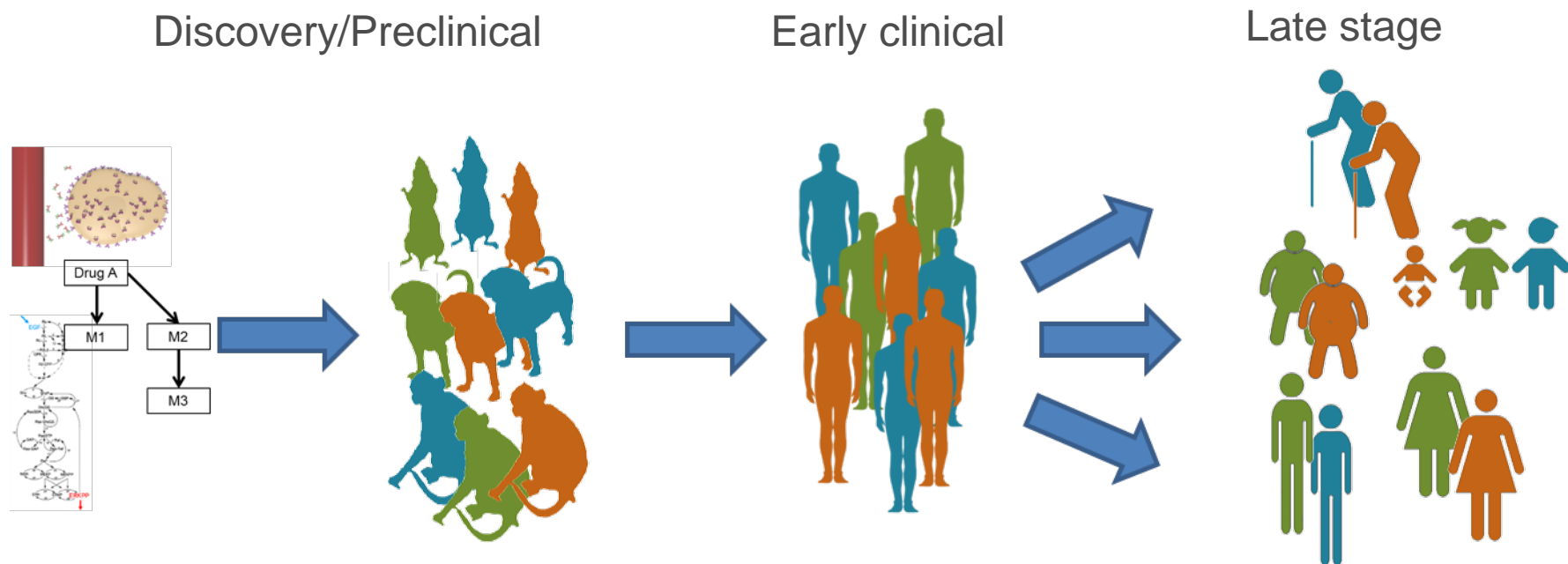
Table:

Alias	Path	Dimen...			Referen
d_endo	Orga...	Length	x	+	Local Refe
SA_p...	Neigh...	Area	x	+	Organism

SA_pls_int*d_endo

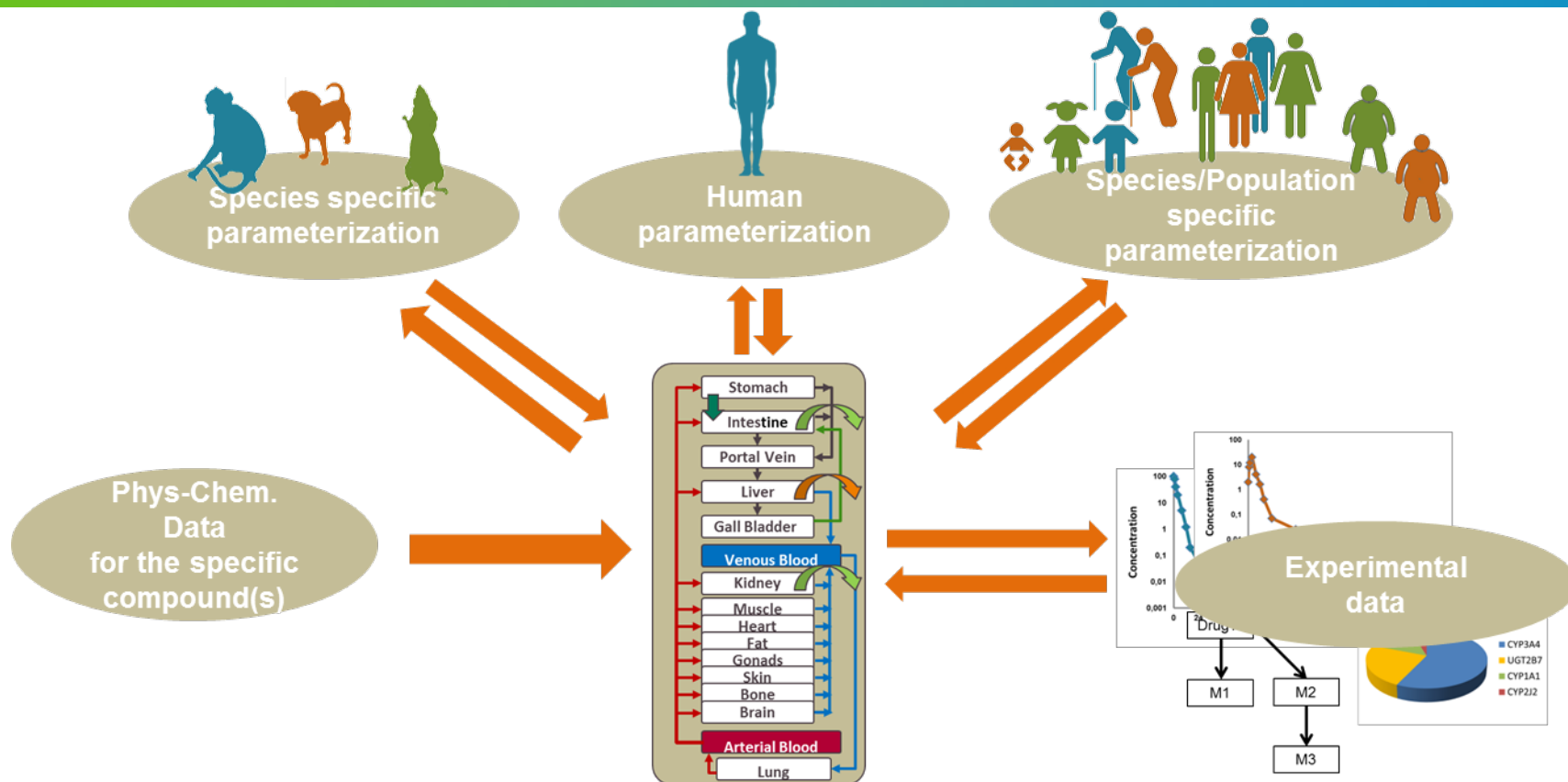
☐ Parameter is state variable

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

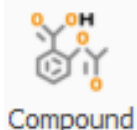
Workflow for PBPK application



Workflow follows development process

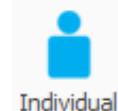
Qualification requires modular concept for the different model components

Modular concept



Physicochemical properties (lipophilicity, molecular weight, pKa)

Drug biological properties (small/large, fu, partition coefficients, permeability, active processes)



Enzymes, transporter, ...

mouse, rat, beagle, monkey, human, ...

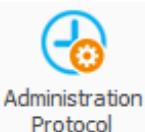


ICRP, NHANES, Tanaka, ...

Healthy, renally impaired, ChildPughA/B/C, other diseased populations

Adults, children, preterm, elderly

Geno/Phenotype (PM, EM, IM),...



Type: IV, PO, ...

QD, BID, Q3W,...

mg, mg/kg, mg/m²...



Dissolved, particle dissolution, empirical functions



Food intake, different meal types, exercise, ...

Why a modular concept?

use of prior knowledge by development with modules

Developed PBPK model



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
 - Literature 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!