Science For A Better Life

PBPK for Paediatric Development

Qualification of the PBPK platform for the Intended Purpose

EMA workshop on qualification and reporting of PBPK modelling and simulation – 2016-11-21 – R. Burghaus

Scope of the Guideline Draft – Paediatric Context

- Guideline scope
  The aim of this guideline is to describe the expected content of PBPK modelling and simulation reports included in regulatory submissions, such as applications for authorisation of medicinal products, *paediatric investigation plans* and clinical trial applications. This includes the documentation needed to support the qualification of a PBPK platform for an intended use. The guideline applies both to commercially available platforms and to in-house built platforms.

- Current main purposes of PBPK
  - to qualitatively and quantitatively predict drug-drug interactions (DDIs)
  - *to support initial dose selection in paediatric trials*
  - to support initial dose selection in first in human trials trials
  - (However, it is expected that the extent of use of PBPK modelling will expand

Paediatric Applications of Different Impact

- 4.2.2. Moderate and low level regulatory impact analyses
  Examples of analyses considered to be of moderate impact include when PBPK is used to *support the dose selection for a PK study* in a specific *paediatric population* (see below). Examples of a low impact simulation could include *pre-study optimization of a PK study design.*

- 4.2.3. *Paediatric analyses*
  The qualification needed for a PBPK simulation of pharmacokinetics in paediatric subjects depends on the impact of the analysis on the paediatric development of the drug and on the clinical consequences of altered exposure to the drug. *Posology recommendations in children that are supported by only limited clinical exposure data and heavily rely on PBPK modelling are considered to be high regulatory impact applications*, while simulations to set initial dose to be confirmed in a clinical study may be considered to be of moderate impact. When qualifying a PBPK platform intended for paediatric dose selection e.g. in a Paediatric Investigational Plan (PIP), the system data and variables accounting for the impact of body size, maturation and other potential co-variates affecting the model predictions need to be specifically justified, presented and discussed. The qualification could include demonstration of accurate prediction of the pharmacokinetics of drugs with similar pharmacokinetic properties as the investigational drug, such as having the same major elimination pathways, e.g., the same metabolising enzyme.

Waiving Paediatric Studies – A High Impact Case

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YASMIN safely and effectively. See full prescribing information for YASMIN.

YASMIN (drospirenone/ethinyl estradiol) tablets, for oral use

Initial U.S. Approval: 2001

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

The data provided reflect the experience with the use of Yasmin (3 mg DRSP/0.03 mg EE) in the adequate and well-controlled studies for contraception (N=2,837). The US pivotal clinical study (N=326) was a multicenter, open-label trial in healthy women aged 18 -35 who were treated for up to 13 cycles. The second pivotal study (N=442)was a multicenter, randomized, open-label comparative European study of Yasmin vs. 0.150 mg desogestrel/0.03 mg EE conducted in healthy women aged 17-40 who were treated for up to 26 cycles.

8.4 Pediatric Use

Safety and efficacy of Yasmin has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

Waiving Paediatric Studies Can be Non-Acceptable even in Simple Cases

- Guideline on the role of pharmacokinetics in the development of medicinal products in the *paediatric population* (EMEA/CHMP/EWP/147013/2004):
  - 4.2.4 Specific considerations for adolescents (✓)
    The pharmacokinetics in adolescent patients is often similar to the pharmacokinetics in adults. In many cases, limited confirmatory pharmacokinetic data are sufficient in this group. Monitoring the onset of puberty (✓) could be considered if it is suspected that inter-individual variability in maturation may be of importance for individualising the dose. Stratification of the patient group according to sex (✓) could also be considered in case gender differences are expected.
- Extrapolation from well studied adult pre-menopausal women to post-pubertal adolescent women in a women's health indication constitutes a *very low translational hurdle*.
- *The respective label claim needed to be based on clinical evidence, still!*

Figure 1. Validation of the PBPK Models for DRSP and EE.[4-6]

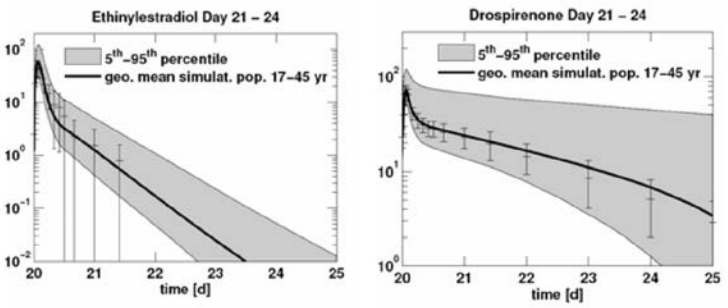
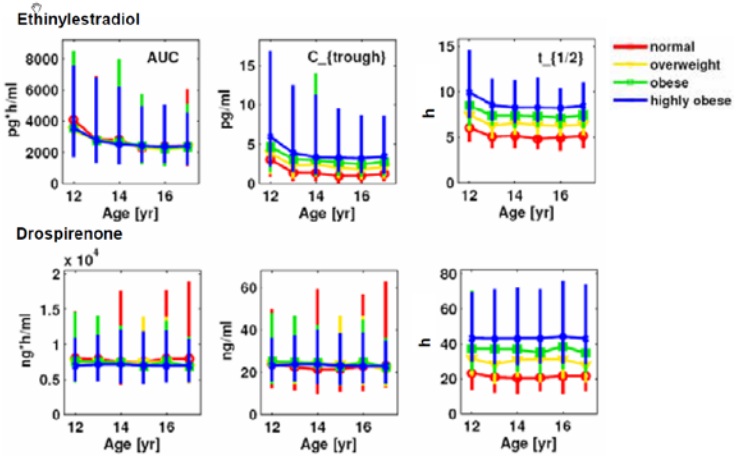
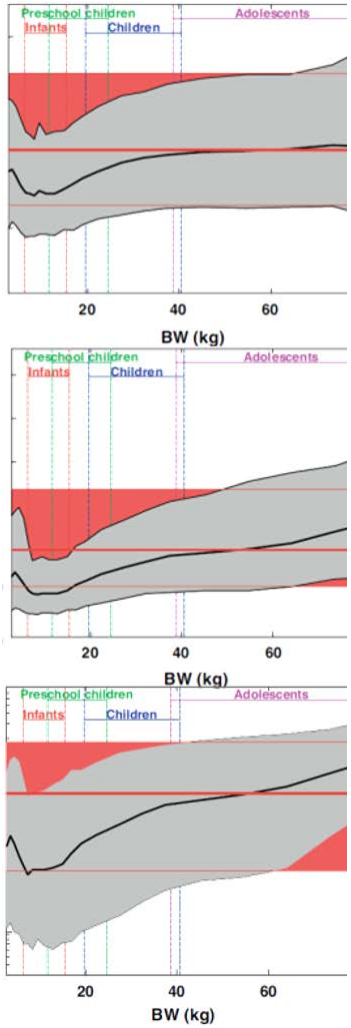


Figure 2. Comparison of steady state PK parameters within the female populations of different BMI



Selection of Doses for Paediatric Trials is a Highly Relevant but Normal Impact Application



adult exposure based dose bridging

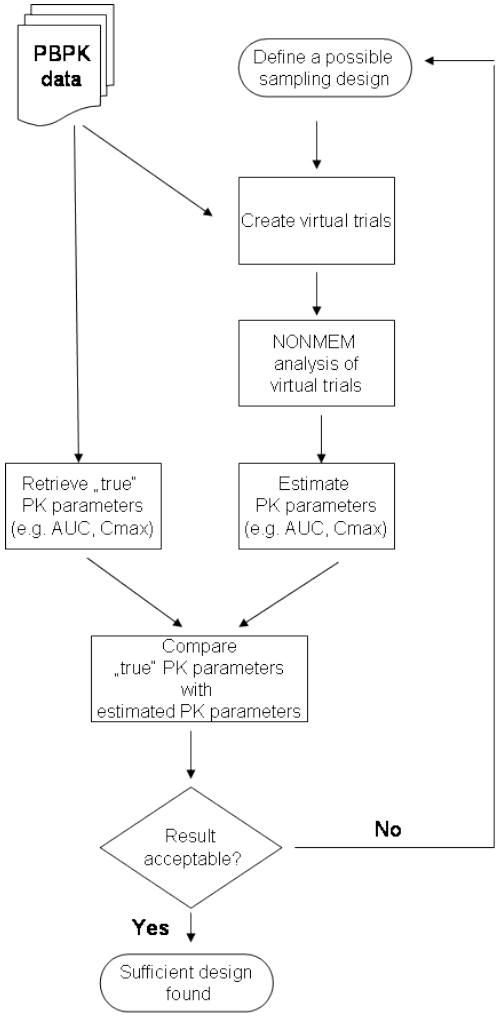
Result: Age and body weight adapted dosing table

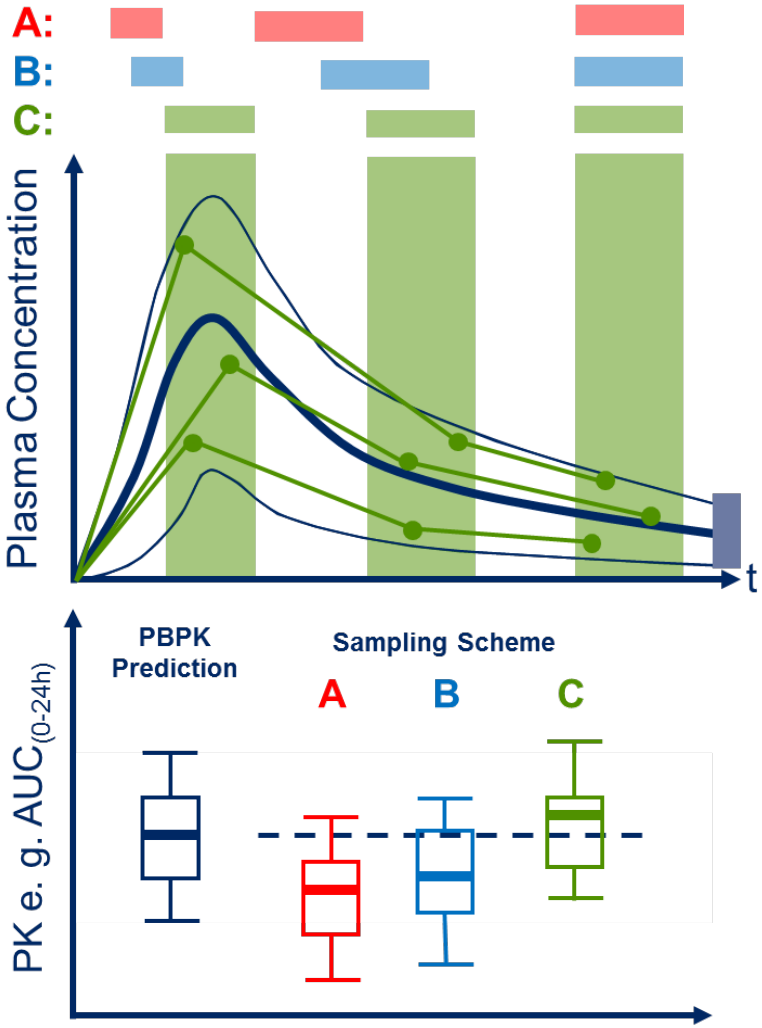
Age group	Body weight [kg]	Dose	
		Tablet	Suspension
Body weight			

Optimization of a PK Sampling Design is Low Impact but of High Operational/Ethical Relevance

Guideline on the role of pharmacokinetics in the development of medicinal products in the *paediatric population* (EMEA/CHMP/EWP/14701 3/2004)

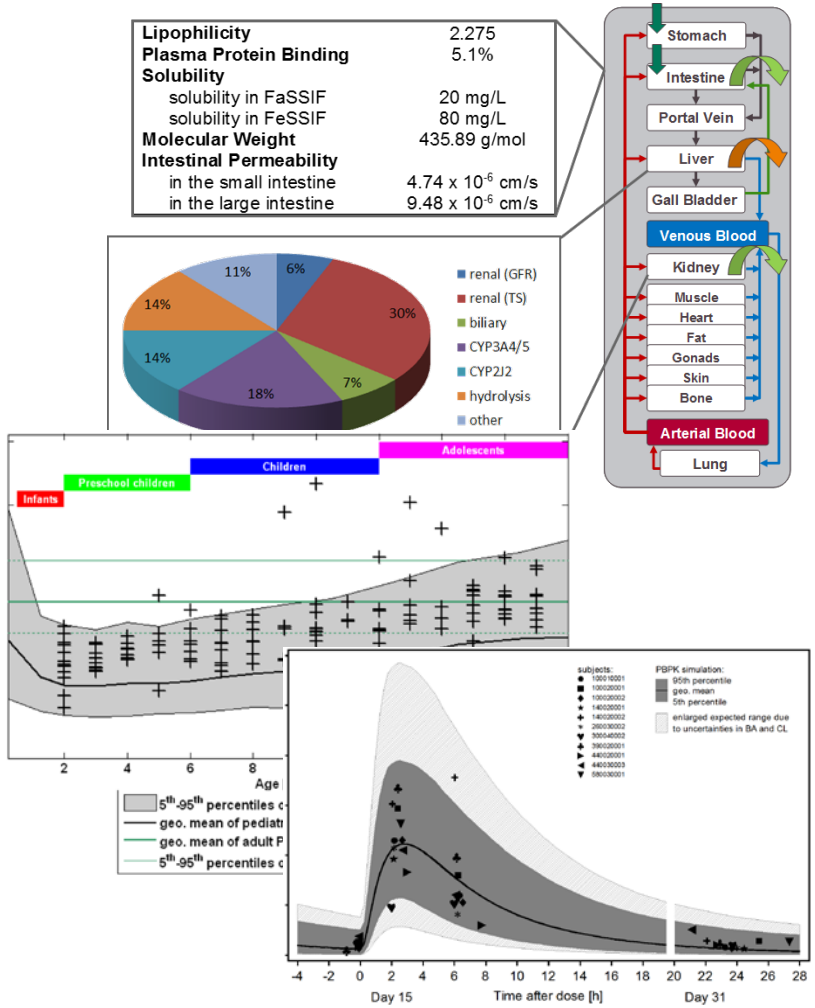
- Simulations or theoretical optimal design approaches, *based on prior knowledge*, should be considered as tools for the selection of sampling times and number of subjects.





Qualification of the PBPK Platform for Paediatric Applications

- Paediatric PK data from controlled trials gets available for an increasing number of novel drugs.
- Specific qualification of the PBPK platform for paediatric applications can be accumulated based on retrospective assessment of predictive performance for different compounds.
- CAVE:
  - Modern drug compounds are designed e.g. for multi-pathway elimination routes in order to avoid relevant DDIs or sensitivities to polymorphisms.
  - Specific paediatric physiological properties can hardly be qualified on a single compound basis.
  - Integrative approaches are required.

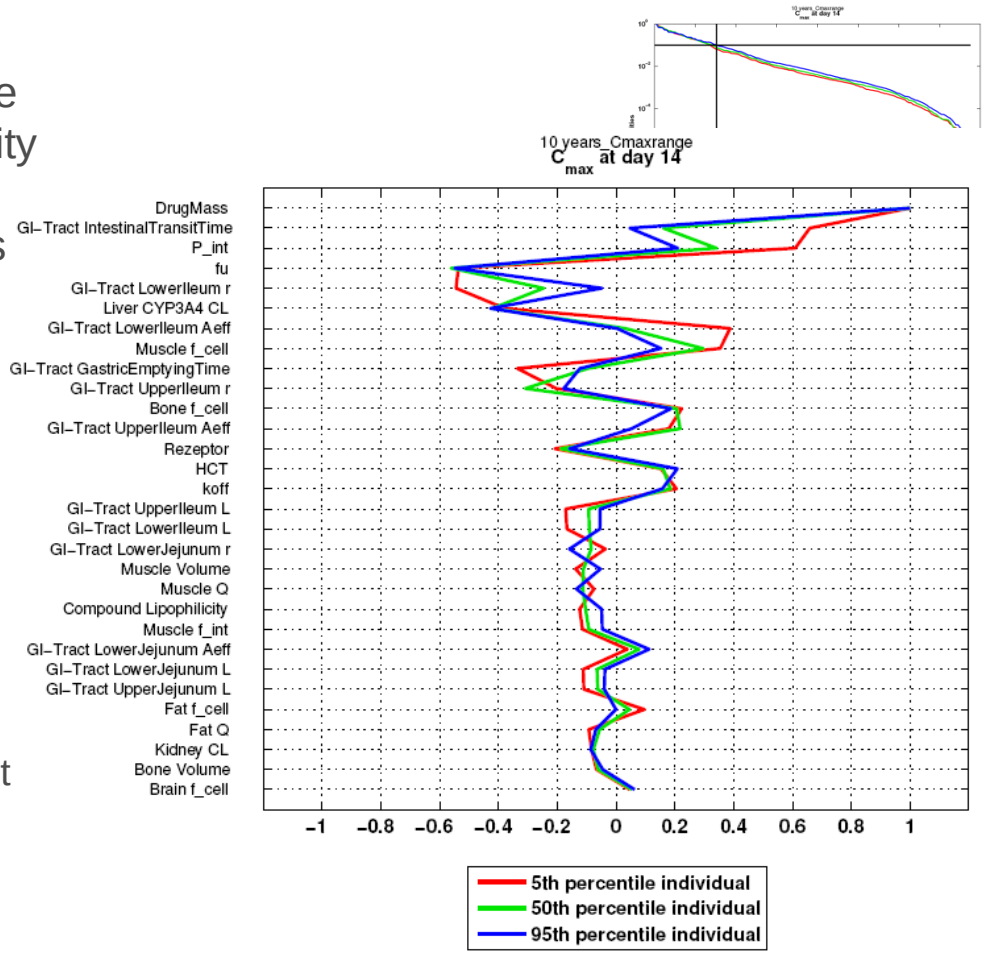


Assessment of Prediction Confidence based on Sensitivities vs. Confidence

- "5.5.4. Sensitivity analysis
  When PBPK is used for simulation in the paediatric population additional sensitivity analysis on the uncertainty related to maturation of enzymes and transporters involved in the elimination should be performed, if relevant."
- A PBPK platform should provide respective workflows, e.g.:

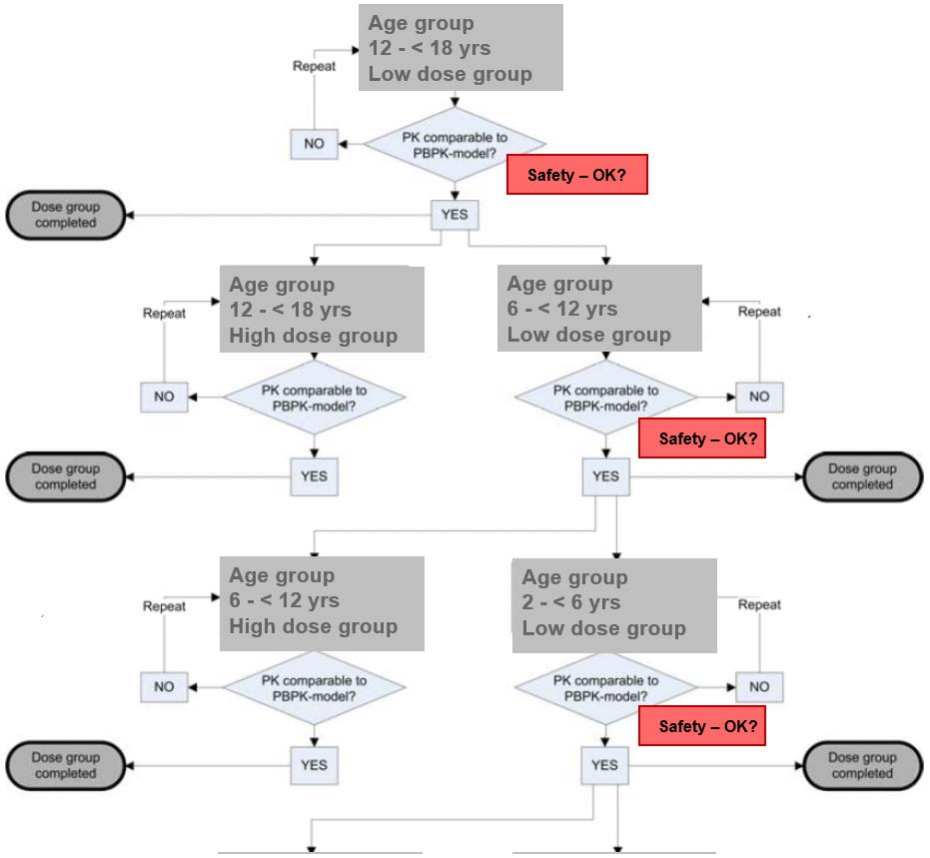
1. Determination of globally normalized sensitivities of all (independent) parameters
2. Determination of cut-off using integral sensitivity threshold
3. Detailed analysis and discussion of dominant "factors" using standard report format

- Sensitivities need to be analyzed in an age dependent manner



Rolling Qualification through an Integrated Age-Staggered Clinical Development Approach

- Organizing paediatric development in an age-staggered fashion enables validating the PBPK model from older to younger age groups.
- In case of discrepancies, the need for dose adjustments in the current and/or subsequent age group(s) can be analyzed based on an updated PBPK model.
- This process reduces the translational distance prior to first dosing of an age group.



“How would you qualify a PBPK platform for an intended purpose, as outlined in the Guideline? Focus should be on a high impact application. How would you qualify the next version of the PBPK platform for the same use ?”

- Qualification for the purpose of paediatric extrapolation should consist of 5 hierarchical levels:
  1. General qualification of the PBPK platform
  2. Specific qualification of the PBPK platform for paediatric applications based on retrospective assessment of predictive performance for different compounds
  3. Specific compound based proof of applicability of general PBPK platform (consistent representation of all relevant in-vitro, pre-clinical, clinical compound data)
  4. Assessment of PK-drivers (sensitivities) vs. confidence in respective physiological paediatric prior information
  5. Rolling qualification through an integrated age-staggered clinical development approach
- High impact PBPK applications in paediatric development is a small niche application due to the specific ethical circumstances in clinical paediatric development.

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

- The current guideline refers to different types of qualification data sets at different locations.
  - Consolidation of general considerations in a dedicated section could facilitate a deeper understanding of the guidance.
- Bayesian concepts for iterative accumulation of physiological posterior knowledge across development programs are emerging. Guidance on how to handle qualification dataset aspects would be helpful.

“Are the approach of the 3 practical qualification processes adequate?”

- Qualification outside of a regulatory submission / CHMP qualification procedure (EMA/CHMP/SAWP/72894/2008/Rev.3)
  - Pro: Simplifies submission package; minimizes regulatory uncertainty for the applicant
  - Con: Time-consuming process; delays for incorporation of scientific advances (including yet unpublished applicant data)
- Qualification within a regulatory submission
  - Con: Increases complexity of submission package; increases regulatory uncertainty for the applicant
  - Qualification established by applicant
    - Pro: Flexible approach; allows submission tailored qualification; allows incorporation of most recent information (including yet unpublished applicant data)
  - Qualification established by „learned societies“
    - Pro: Leverages information, data, expertise of society members; reduces regulatory uncertainty for the applicant (does it?)

“What changes would you propose?”

- “Learned societies” have a potential to become impactful players in advancing PBPK know how for paediatric applications. Please elaborate on:
  - What qualifies as a “*learned* society”?
    - Open community approaches could facilitate collaboration between regulatory, academic and industrial experts and stakeholders with low hurdles and maximum transparency. What could be organizational design elements of an open community to qualify as a “learned society”?
  - What is the regulatory acceptance of a “learned society” qualification vs a single applicant qualification?
- In paediatric development, most PBPK applications are and will be of medium (or low) impact. More explicit specification wrt differences in regulatory qualification expectations would help applicants.
- We understand qualification of a PBPK platform as an element of the execution of a PIP, rather than a prerequisite for its acceptance. Clear wording would be beneficial.

“What changes would you propose?”

- Given the modular nature of PBPK M&S, we propose to account for the different nature of:
  - PBPK substance model building
    - Model building is implemented as a continuous learning activity integrated into the drug development process (pre-clinical, early clinical, late stage clinical). Reasons for inclusion of experiments/studies are identical with the respective PK related experiment/study objectives.
    - Objectives are to challenge the consistency of all experimental evidence with our understanding of PK properties of the compound and physiological prior knowledge and to provide a fully integrated and executable representation of our PK understanding and information.
    - The substance model is reported independent of application intend (e.g. paediatric extrapolation).
  - Specific applications of PBPK substance models (simulation), e.g. special populations/*paediatrics*, DDI, special dosing scenarios, etc
    - Model applications/simulations have specified objectives.
    - Qualification and reporting is done wrt the intended purpose (objective).

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Thank you!