EMA Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modeling and simulation

Viera Lukacova

Simulations Plus, Inc.

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Outline

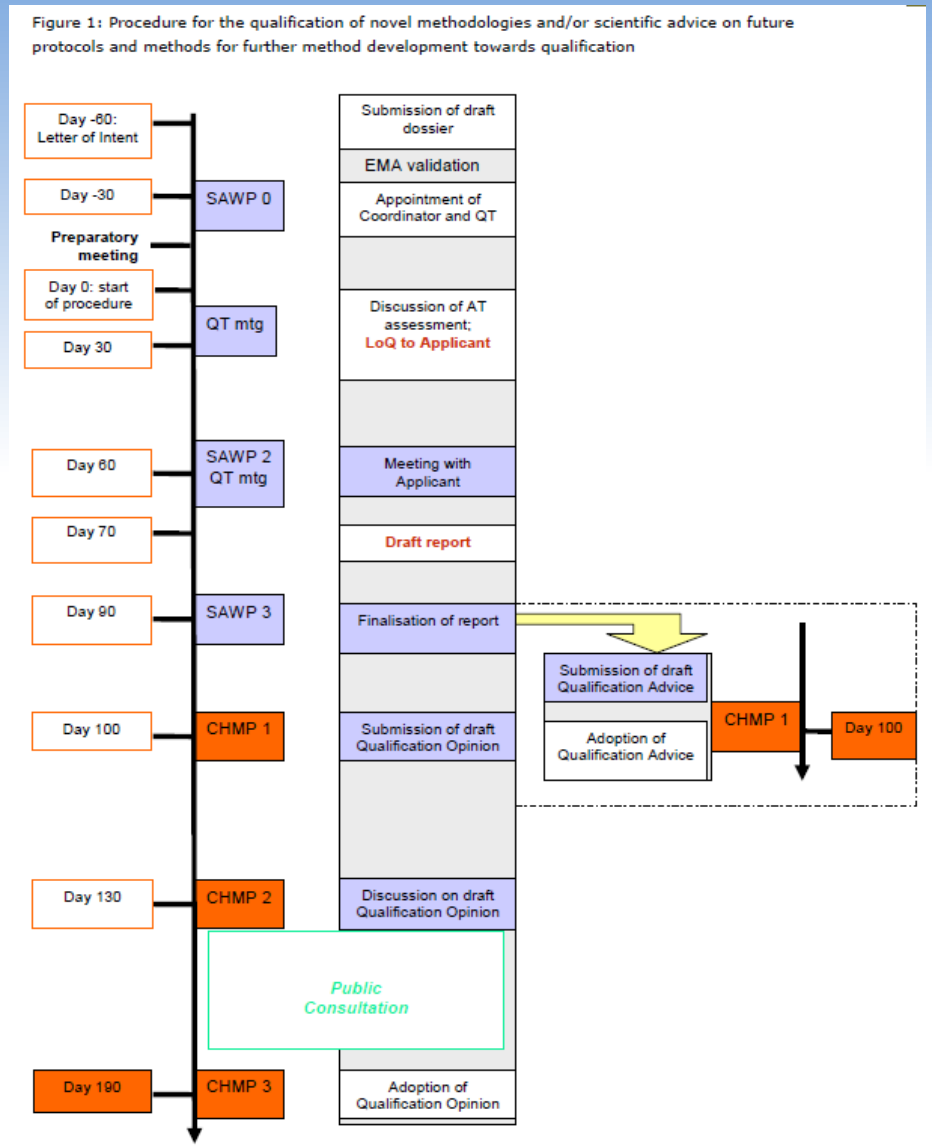
We have been asked to address following questions:

- Are the approaches of the 3 practical qualification processes (CHMP procedure, qualification for specific purpose, and a recommendation from learned societies) adequate? (Please discuss pros and cons of the different processes)
- How would you qualify a PBPK platform for an intended purpose, as outlined in the Guideline? (Preferably with examples). Focus should be on a high impact application. 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? (Please discuss)
- In a constructive way - what changes would you propose?

Qualification Process

Approach 1: CHMP Procedure

- Would make subsequent applications easier:
  - Straightforward application of qualified platform for given purpose
  - Higher confidence in the outcome from sponsor companies
  - Fewer resources required at regulatory agency to review subsequent applications
- Very lengthy and very expensive process
  - Especially if different types of applications need to go through separate qualification procedures



Qualification Process

Approach 1: CHMP Procedure – cont.

- Before starting the qualification process need more information on:
  - How much software capability can be covered in a single CHMP application?

    For example:
    - Can software be qualified to predict absorption in general or would it have to be split for different drug subgroups (high/low permeability compounds, compounds with high contribution of paracellular absorption, etc.)
    - Can software be qualified for metabolism- or transporter-based DDI in general, or specific to certain types of compounds? Would the model for every standard compound supplied with the software have to be qualified separately?
  - Need a clear path for qualification of subsequent program versions:
    - Will a complete CHMP procedure be required with each new version of the program or could it be a simpler comparison of results with previously qualified version?
    - What would be the cost of the requalification through the CHMP procedure?

Qualification Process

Approach 2: For specific purpose within application:

- Could be faster to compile the information for a specific application
- More uncertainty in the outcome – less confidence in the outcome from the sponsor companies
- Less efficient for the regulatory agency - reviewers may end up reviewing the same information repeatedly

Approach 3: Recommendations through learned societies:

- Software providers have very little influence on the process
- Can EMA provide guidance on the type of publication and detail needed in the publication for it to be sufficient for qualification process

Qualifying PBPK Platform

- Scientific qualification: Are the models (equations) implemented in the software predictive?
  - Physiological information – we will provide a confidential report on the sources of physiological parameter values for built-in physiologies
  - Population simulations – we will provide confidential comparison of physiologies generated by the program and reported physiological variabilities
  - Compound models included with the software – we will provide reports describing the compound models (input parameters, *in vivo* data used to calibrate and validate the compound model)
  - We are in the process of reviewing and compiling information from publications with GastroPlus™ applications for examples that could be supplied as additional support for model predictions

Qualifying PBPK Platform

- Technical qualification: Is the code doing what it is supposed to be doing?
  - It is a part of the standard QC process for each version release
  - We can compile the information in the format that could be submitted with the application
  - Does this need to be submitted automatically with every fit-for-purpose application or just have it available to provide upon request from the agency?
- It seems that the same documentation needs to be prepared for either CHMP procedure or qualification for specific purpose
- Decision on whether to proceed with full CHMP qualification procedure will depend on the responses to questions raised in previous slides
  - Resources for Approach 1 would not be trivial - will have to be covered somehow
  - Consideration of cost/benefit – what is reasonable and adequate?

Example of Platform Qualification: Pediatric Predictions

- Provide the summary of physiological parameters in pediatric physiologies
- Show accuracy of pediatric predictions for compounds eliminated by a specific pathway.
- For each validation compound, include summary of:
  - Compound-specific input parameters
  - Model calibration and validation in adults
  - Accuracy of predictions in different pediatric groups
    - Ideally, full plasma concentration-time profiles would be used to evaluate the accuracy of prediction
    - If Cp-time profiles are not available (often not reported in public sources) a comparison could be made on the basis of available PK endpoints (AUC, CL, Vss, etc.)

Qualifying Next Versions

- How to qualify the next software version:
  - Clearly describe the changes in the new version
  - Focus on requalifying only the parts of the program which have changed
    - Requalifying of the sections of the program that changed – rerun test cases to ensure that the modification resulted only in intended changes and improved predictions where applicable
    - Remaining sections of the program – rerun test cases to show that unintended changes were not introduced
- Qualifying updated compound models supplied with the software:
  - Describe the changes in the model and explain why the model was changed (i.e., more accurate values for input parameters became available, etc.)
  - Describe and demonstrate the performance of the updated compound model

Qualification Datasets

- The guidance asks for large qualification datasets:
  - What is considered to be a “large” dataset?
  - Higher emphasis should be placed on diverse (where applicable) rather than large dataset.
- Datasets for DDI predictions are described in detail:
  - To qualify inhibitor models, need to show predictions with qualified substrates; to qualify substrate models, need to show predictions with qualified inhibitors … where do we start?
  - How many different substrate models are required to qualify the inhibitor models and vice versa?

Proposed Changes: Define Validation

- What constitutes validation?
  - Use of part of observed data to calibrate model, then prediction of remaining observations with reasonable accuracy without modifying the model
    - Recognition that variability in biological systems does not allow for perfect predictions – “adequate, not perfect” should be the criteria
      - Adequate means a level of accuracy sufficient to make well-informed project decisions
      - Recognition that simulation and modeling never stands alone – always considered in light of numerous other bits of information
  - Generating artificial “data” with known outcomes and verification that the known outcomes are predicted
    - Provides a way to validate equations without the variability in observed data

Proposed Changes

- The guidance focused on DDI applications … it should include a stronger statement that applications in other areas are possible
- More detailed specification on what is considered to be acceptable model performance
- If sponsor company did not use the latest version of the platform, they are required to justify this decision. This may be difficult:
  - Companies go through strict internal validation of each new software version before it is released for use by scientists: there may be several months delay between the release of a new version and when the new version is available to scientists.
  - There might be a change in a relevant section of the platform and the change was not requalified yet.
  - There might be changes in the underlying model that affect the simulation result.