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Concept paper on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and analyses

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Comments should be provided using this template. The completed comments form should be sent to PKWP@ema.europa.eu.

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1. Introduction

This Concept Paper proposes the drafting of a guideline on how to report the results from and performance of a Physiologically-based Pharmacokinetic (PBPK) analysis. PBPK analysis is utilised in a growing proportion of applications for marketing authorisation of new chemical entities. Systems pharmacology models in general are expected to become more important in drug development.

PBPK is presently mentioned in several guidelines including the *Guideline on the Evaluation of the Pharmacokinetics of Medicinal products in Patients with Impaired Hepatic Function* (CPMP/EWP/2339/02), the *Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products* (EMA/CHMP/37646/2009) and the *Guideline on the investigation of drug interactions* (CPMP/EWP/560/95/Rev. 1 Corr.*). PBPK will also be included as a tool in upcoming new guidelines and guideline revision applications for marketing of new chemical entities.

2. Problem statement

Available EMA guidance covers the principles and the general approach to the use of PBPK analysis. The *Guideline on the Investigation of Drug Interactions* and the *Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products* also include general advice regarding qualification requirements. However, there is no detailed guidance on the expected level of reporting of the analyses nor on what should be included in the report to show the performance of the system (e.g. software) and the limitations of the models in simulating a given scenario. This lack of clear advice to applicants is reflected in differing levels of reported detail, which can preclude adequate assessment of the modelling.

3. Discussion (on the problem statement)

Guidance is needed on how to qualify and present the results of a PBPK modelling analysis, in order to provide sufficient detail to enable regulatory authorities to properly assess the analysis and its conclusions. At present, the submitted reports are of variable quality and may not contain the information needed to evaluate the performance of the model. PBPK analysis can be performed using several different commercially available or in-house programs which may differ in how they present the results of the analysis and in how robustly they support the adequacy of the model. The guideline will give general advice applicable to the contents of PBPK reports and qualification of PBPK models in general.

Evidence needs to be provided to demonstrate the predictive performance of the system for its intended purpose (system model qualification). PBPK models are complex, consisting of the system (e.g. equations and physiological parameters, the so called “system dependent parameters”) but also sometimes libraries of specific drugs and their parameters, as well as modelling data for populations with different characteristics. If library drugs data included in the software are used in the analysis, the adequacy of the library files needs to be supported. In addition, since the software modelling is complex and involves a large number of equations, there is a risk that when new versions of software are published, this may lead to changes in the predictions. The capacity to perform adequate predictions in the version of the system used in the study needs to be confirmed.

The basis for all input parameters, their biological plausibility, uncertainty around their measurement or calculation and details on optimisation process or updating undertaken based on in vivo data should be presented. One consequence of the complex system models with numerous drug-dependent input

parameters is that multiple combinations of drug-dependent parameter values will equally well predict the observed plasma concentration-time data. The choices made need to be justified and consequences for simulations discussed. Finally, the ability of the model to simulate the PK behaviour of the drug needs to be shown (verification of drug model).

In a PBPK report, the performance of the PBPK model used needs to be supported, i.e. it must be shown to be qualified for the particular purpose. The drug-dependent parameters need to be supported and how well the drug´s in vivo PK behaviour is predicted needs to be shown. Furthermore the ability of the full model to adequately predict behaviour in particular study situations for a specific drug, or subpopulations (i.e. DDI, paediatric, geriatrics) needs to be substantiated.

It should be emphasised that the requirements on modelling and simulation methods are dependent on the intended use of the model, e.g. the demands on model evaluation increase with the relative importance of the analysis. The requirements of a simulation may also be dependent on the therapeutic window of the affected drug. This will be further discussed in the guideline.

4. Recommendation

It is recommended that a CHMP guideline is developed to provide guidance on what should be included in PBPK reports including model qualification. Aspects suggested to be considered when drafting the guideline are listed below:

- Purposes of the simulation including regulatory use
- Qualification of the system i.e. the predictive performance of the system for the particular purpose
- Version control of the system and support of its predictive performance
- Justification of assumptions made and impact on the results
- Justification of system parameters incl. library files, physiological parameters of population
- Justification of drug parameters
  - Description of model building
  - Summary of parameter and sources (i.e. mean, known or predicted variability)
  - Data needed to support model building
- Justification of any adaptation of the model to optimise the fit of the simulation to in vivo results
- Sensitivity analysis of uncertain parameters
- Verification of drug model
  - Predictability of the model of in vivo pharmacokinetic characteristics including several representative PK studies, nonlinearities, etc.
  - Diagnostic plots
- Ability of the full model (drug + system) to predict the intended situation; e.g. prediction of available in vivo study data or data in subpopulations such as poor metabolisers, in vivo data on linearity
- Presentation of the simulation results
  - The details of all simulation conditions

- Outcome of sensitivity analysis of uncertain parameters
- Relevant pharmacokinetic parameters (e.g. AUC, Cmax, $t_{1/2}$, Cmin, interaction ration, including inter-individual variability)

- Submission of model files in an executable format

Conclusions and implications of the results taking available data on exposure-response/safety into account.

5. Proposed timetable

The Concept Paper will be released for 3 months external consultation. Following the receipt of comments, the draft Guideline will be consolidated and released for 6 months external consultation.

6. Resource requirements for preparation

The preparation will mainly involve the Pharmacokinetics Working Party (PKWP) and the Modelling and Simulation Working Group (MSWG).

7. Impact assessment (anticipated)

The most important anticipated impact of a guideline on the reporting of PBPK analyses lies in more informative reports that allow for a satisfactory assessment of the analyses. The guideline may also be expected to impact execution of these analyses by explicitly setting out regulatory standards. It is also envisaged that regulatory confidence in extrapolations based on PBPK could increase, as the evidence base supporting the validity of specific applications of PBPK (e.g., DDI, paediatrics, geriatrics) is systematically and consistently strengthened.

8. Interested parties

Academia, international scientific societies, pharmaceutical industry.

9. References to literature, guidelines, etc.

Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr.*).

Guideline on the Evaluation of the Pharmacokinetics of Medicinal products in Patients with Impaired Hepatic Function (CPMP/EWP/2339/02).

Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009).

IPCS Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment (WHO).