EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	***pharmacokinetics, modelling, simulation, qualification, predictive performance***

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Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Table of Contents

Executive summary

A growing number of regulatory submissions include physiologically based pharmacokinetic (PBPK) models that require the use of specialised software platforms. While PBPK modelling is presently mentioned in several existing EMA guidelines, this is the first to specifically provide detailed advice on what to include in a PBPK modelling report including, in particular, details of the predictive performance of the drug model. If PBPK modelling is intended to support a regulatory decision, the PBPK platform needs to be qualified for the intended use. This document, therefore, also aims to clarify which supportive data are expected in order to qualify a PBPK platform, accordingly.

1. Introduction

For the purpose of this guideline, a PBPK model is defined as a mathematical model that simulates the concentration of a drug over time in tissue(s) and blood, by taking into account the rate of the drug's absorption into the body, distribution in tissues, metabolism and excretion (ADME) on the basis of interplay between physiological, physicochemical and biochemical determinants. Presently, the main purposes of PBPK models in regulatory submissions are to qualitatively and quantitatively predict drug-drug interactions (DDIs) and to support initial dose selection in paediatric and first-in-human trials. However, it is expected that the extent of use of PBPK modelling will expand as additional scientific evidence on e.g. physiology parameters in different populations (system knowledge) is gained and confidence in the utility of PBPK models increases.

The majority of PBPK regulatory submissions currently involve the use of commercially available specialised PBPK platforms, i.e. collections of computer programs and included system data. However, the recommendations in this guidance apply to both commercially available platforms and non-commercial/in-house built platforms. In any event, when used for regulatory decisions, simulations performed using PBPK platforms need to be carefully assessed regarding (1) the ability of the platform to adequately perform simulations of the intended type (i.e., the PBPK platform needs to be qualified for the intended use with well characterised in vivo data) (see Appendix 1) and (2) the predictive performance of the specific drug models (see Appendix 2). To allow for such assessment the submitted PBPK report should include the validity and biological plausibility of input parameters, the uncertainty around the determination or prediction of parameter values, clarity on the model building and optimisation processes, and a discussion of the consequences of the assumptions made. The level of the evaluations depends on how much weight of evidence the PBPK simulation will have in the decision making i.e. the regulatory impact (see Appendix 1).

If PBPK modelling is used in the development of an investigational drug, it is strongly recommended to use the opportunity to optimally design clinical pharmacology studies that can provide data to progressively improve the model and support the planned model applications.

For the qualification of PBPK platforms for an intended purpose, Committee for Medicines for Human Use (CHMP) scientific advice (Qualification of novel methodologies for drug development: guidance to applicants EMA/CHMP/SAWP/72894/2008/Rev.3) may be sought. Qualification may also be supplied in a given regulatory submission where the PBPK modelling is applied. Qualification may also be supported by, e.g. peer reviewed literature. Seeking CHMP Scientific Advice for additional guidance on the use of PBPK modelling and simulation in support of regulatory decisions is encouraged.

2. Legal basis

This guideline should be read in conjunction with Directive 2001/83/EC as amended. Applicants should also refer to other relevant European and ICH guidelines, including those on:

- Investigation of drug interactions (CPMP/EWP/560/95/Rev. 1).
- Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products. (EMA/CHMP/37646/2009).
- Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CHMP/EWP/225/02).
- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02).
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004).
- Guideline on reporting the results of population pharmacokinetic analyses (EMEA/CHMP/EWP/185990/2006).

3. 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 PBPK platform for the intended use and the evaluation of the drug model. The guideline applies to commercially available platforms and to in-house built platforms.

Regulators' particular considerations to allow for a thorough assessment of these models are highlighted. For specific scenarios where PBPK models may be applied, additional clarifications are given together with examples of suitable approaches.

4. Reporting of PBPK modelling and simulation

The key areas to be addressed in a PBPK report to enable assessment by regulators are outlined below:

4.1. Objective and regulatory purpose

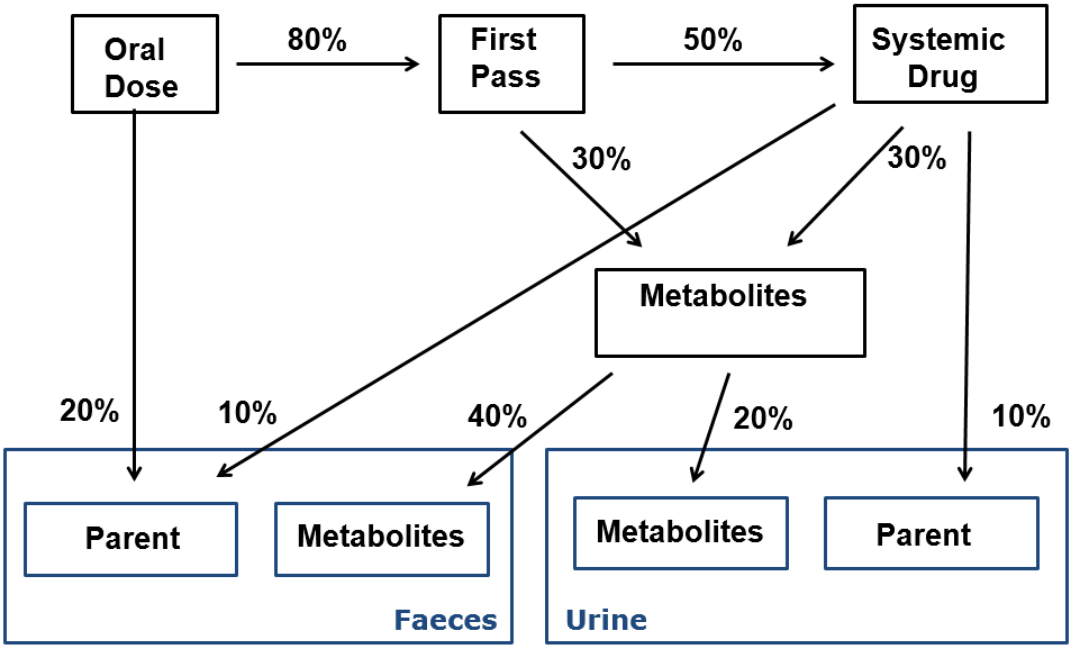
The objective and the intended regulatory purpose of the PBPK modelling, including any proposed information for inclusion or changes to the Summary of Product Characteristics (SmPC), should be clearly described at the start of the report.

4.2. Background information

The introduction of a PBPK report should include the relevant information about the investigational drug relevant for the model, like physicochemical properties. This should emphasise *in vivo* and *in vitro* ADME, or, if applicable, therapeutic protein specific parameters, like extravasation, FcRn recycling, and target mediated disposition and other pharmacokinetic parameters of the drug. A summary of clinical studies should be included. The data included should be related to the intended purpose of the model. A quantitative mass-balance diagram (Figure 1) presenting elimination

pathways with involved enzymes and transporters should be included along with explanatory text and references.

Figure 1: Example of a quantitative mass balance diagram after oral administration of drug, showing contribution of drug absorption, first-pass drug loss and the contribution of different elimination pathways to the overall clearance of the drug[1].



Additional information of relevance for the PBPK model could include data on solubility, permeability, potential dose- or time-dependent pharmacokinetics, drug-drug interactions and effects due to pharmacogenetic differences.

For biopharmaceutical applications, a full description of drug substance and product properties is of importance e.g. particle size, form, solubility and dissolution data at physiological relevant pH values and media.

For paediatric applications an overview of available pharmacokinetic information in other age groups, such as older children and adults, should be presented. Effects of ontogeny such as potential quantitative changes in the contributions of the various elimination pathways in paediatric age subsets should be addressed.

The report should include sufficient background information to place the PBPK modelling in context in the clinical development of the drug. The background information should also contain a summary of the available knowledge about the exposure-response relationship for efficacy and safety and/or the exposure level at the therapeutic dose in the pivotal efficacy/safety trial population. If possible, a well justified target plasma exposure (a range for relevant exposure parameters specifying what change in exposure would justify a posology adjustment) should be defined.

[1] Shepard T, Scott G, Cole S, Nordmark A, Bouzom F. Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation. *CPT: Pharmacometrics & Systems Pharmacology*. 2015;4(4):221-225. doi:10.1002/psp4.30.

4.3. Qualification

The qualification of the platform for its intended purpose should be presented and justified. Experience of qualification of models is limited at the current time however some recommendations with examples are detailed in Appendix 1. This is likely to evolve as more data becomes publicly available.

Where a CHMP qualification opinion or advice has been obtained, a link to this on the EMA website should be submitted.

If commercial software is concerned, the name and version of PBPK platform used should be stated and any subsequent modification clearly documented.

4.4. Model parameters

4.4.1. Assumptions

An explicit and systematic discussion of the assumptions made in the submitted system and drug model and in the associated analysis should be provided. Data to support the assumptions and their biological and/or pharmacological rationale should be presented and discussed, as well as the impact the assumptions have on the model and the outcome. A better contextual understanding of what might be expected if important assumptions are incorrect may be obtained through testing alternative values, with modified models or via a sensitivity analysis of the relevant parameters (see Section 4.7.1). The approaches used to test the assumptions and the outcomes should be presented.

4.4.2. System-dependent parameters

The system-dependent parameters, including physiological parameters for the population(s) for which qualification is claimed, should be presented and justified. Any modification of default values of system-dependent parameters of the dataset should be highlighted. Literature references should be provided as full articles and the rationale for the chosen system-dependent parameter values should be given. The data should be presented in an appendix to the report in a structured way to allow assessment

Any modification of the default values of system-dependent parameters of the dataset should be summarised and justified e.g., changing the values of the degradation constant (k_{deg}) of metabolising enzymes (Guideline on investigation of drug interactions, CPMP/EWP/560/95/Rev. 1). For paediatric modelling the effect of ontogeny and allometry on system values e.g. renal function or albumin concentrations, could be justified using a worst case approach supported by peer reviewed references.

4.4.3. Drug parameters and the drug model

The PBPK report should include a thorough description of the drug model structure and drug-dependent parameters.

A summary of the drug-specific parameter names and values (mean with known or predicted variability: SD or range [min-max]), and the sources of the values should be included in a tabular format. The value of the drug-specific parameter should particularly be justified in the text.

The parameters described should include physicochemical properties and ADME data that were used to parameterise the model. If there is more than one source of a parameter with notably different values, the value chosen should be justified and the consequences discussed.

Some parameters in the model can be either experimental or predicted (e.g. f_{umic}, log D). If there is a range, the dependence of the model for such parameters should be assessed. If such a parameter is considered important for the model it should preferably be measured or otherwise justified as to why this is not possible, or the predicted value is considered more accurate.

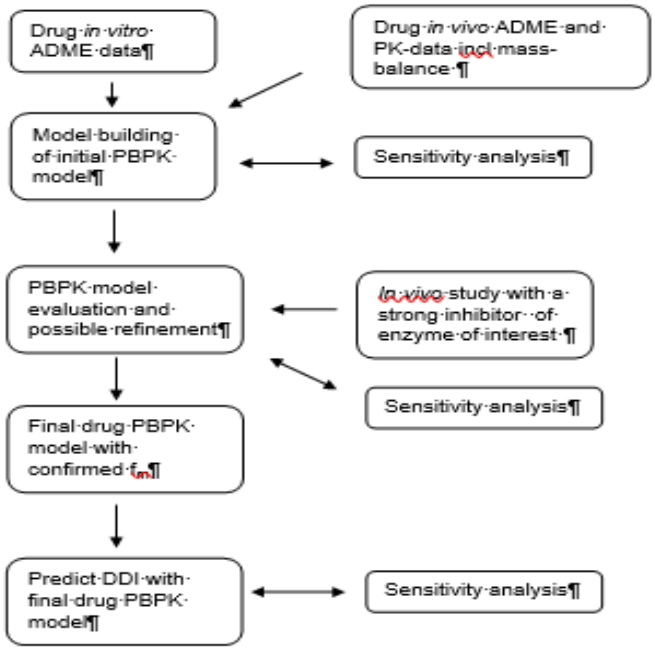
For estimated parameters, the chosen estimation method/procedure must be described, such as the used objective function, minimisation method and error models. Estimated parameter values should also be discussed with regard to their range of known values, biological plausibility and precision of estimation.

Consideration should be given as to whether there are drug specific parameters in the model that are correlated (such as K_i and k_{inact}). If more than one of the unknown parameters are estimated through fitting of the model using observed clinical data, there is a risk that these parameters cannot be uniquely identifiable. In the case that an identifiability issue is suspected, additional *in vitro* or clinical data may be required to increase certainty, on one or both of the parameters. A description on how any identifiability issues have been handled should be given.

4.5. Model development

The building of a PBPK model is an iterative process that includes construction, parameter loading, verification, modification and evaluation of the model prior to its application (see Figure 2). The use of an analysis plan is recommended. An overview of the model building process should be submitted and. any adaptation of the model to optimise the fit of the simulation to *in vivo* results should be described with respect to its rationale and outcome.

Figure 2: Example of a DDI model: modelling workflow overview



4.6. Simulation of the intended scenario

A description of the design of the study to be simulated as well as the target virtual population should be provided. This should include, but not be limited to, dosing information, length of study, number of

individuals and characteristics of the virtual population. The appropriateness of the virtual population should be justified.

4.7. Platform and drug model evaluation

A comprehensive summary of the system and drug model evaluation should be provided.
A thorough evaluation of the drug model is important if the model is to be used to simulate novel situations, e.g. a drug interaction or pharmacokinetics in an alternate population. An evaluation of the model should be presented in sufficient detail in the report to support confidence for regulators in the application of the model in their decision making (Appendix 2).

4.7.1. Sensitivity analyses

An understanding of the confidence in the platform can be assessed with the use of a sensitivity analysis. Sensitivity analysis in this context can be broadly described as a systematic investigation that leads to an understanding of how quantitative changes in key model input parameters (both system and drug dependent parameters) due to inherent variability or uncertainty in measurement can influence the model output and thus characterises the level of confidence in the output.

Sensitivity analysis should be undertaken for parameters that are considered to be key to the model (i.e. that are likely to markedly influence the outcome) or parameters that are uncertain. Examples of parameters considered uncertain are: parameters that are subject to important assumptions, key experimentally determined parameters, parameters with a variety of values reported in the literature, parameters which have been optimised during the model building process, and parameters that are difficult to experimentally determine. The range of the parameter values to be tested should be pre-specified and the range should be justified based on scientific rationale, published data or known variability in the estimate. A 'worst-case' approach is recommended e.g. for CYP enzymes 10-fold, for transporters 30-fold. To allow for assessment of the impact of correlated parameters, a global approach may be performed. Otherwise a joint sensitivity analysis, where two or more parameters are tested simultaneously, may be the preferred choice.

Sensitivity analysis should be performed both during the development and application of the drug model (Figure 2). For example, for PBPK models of investigational drug when used to predict inhibition of an enzyme, sensitivity analysis should be performed on the interaction parameter Ki (Guideline on investigation of drug interactions CPMP/EWP/560/95/Rev. 1). For PBPK models where the absorption is of importance, parameters which may impact drug absorption should be subjected to sensitivity analysis such as gastrointestinal pH, particle size and other parameters that are uncertain or that cannot be measured such as unbound concentration in the enterocyte. When PBPK is used for simulation in the paediatric population additional sensitivity analysis related to ontogeny of enzymes and transporters involved should be performed, if relevant.

An alternative approach to understanding the robustness of the model output could involve the use of an integrated population PBPK approach where uncertainty of parameters and known variability is incorporated in the model.

4.7.2. Evaluation of the predictive performance of the drug model

The drug model must be shown to be capable of predicting the observed pharmacokinetics of the compound before the model can be used for simulations of special situations. Details on how this can be evaluated are shown in Appendix 2.

4.8. Results

The results of the model evaluation and final simulation(s) should be presented in a clear and comprehensive manner. The relevant simulated pharmacokinetic parameters (e.g., AUC, C_{max}, $t_{1/2}$, C_{min}, V, CL, accumulation / interaction ratios, and inter-individual variability) should be tabulated and presented visually using figures and graphs. The parameter values should be reported with descriptive statistics such as geometric mean and standard deviation and/or range.

The relevant model files that were used to generate the final PBPK simulations (including compound and population files) should be provided in a tabular format in the report as well as submitted electronically separately in an executable format.

The outcome of performed sensitivity analysis should be provided (see Section4.7.1.).

4.9. Discussion of the regulatory application

The contribution of the PBPK modelling and simulations to the regulatory decision making and the regulatory use should be explicitly stated. The confidence in the model predictions should be considered before conclusions are drawn based on the model, and it should be discussed how the potential uncertainty may influence the decision making.

Definitions

Computational model/solver: Parts or algorithms included in the computing platform that numerically solves the mathematical model.

Drug specific parameters: Physiochemical properties, *in vitro* and *in vivo* ADME parameters, pharmacokinetic characteristics.

Drug model structure: The structure, i.e. framework of compartments, of the PBPK model (including absorption model, perfusion- or permeability-rate limited organ distribution models, number of distribution compartments, connecting organ blood flows, etc.).

Parameter identifiability: There is sufficient information in the experimental input–output design to uniquely identify model parameters.

Compound files: Compound PBPK files supplied within a platform (e.g., inhibitors, inducers and substrates).

Mathematical model: The underlying equations proposed to model a process.

PBPK platform: The in silico platform used, i.e., a collection of computer programs and included system data. This includes the model structures, mathematical model, computational model, system dependent parameters including library compound files, etc.

Predictive performance of drug model: The process of establishing confidence in the drug model. The reliability is assessed on the basis of how well important characteristics of the drug model has been tested against *in vivo* pharmacokinetic data and whether adequate sensitivity and uncertainty analyses have been conducted to support the models ability to provide reliable predictions.

Qualification: The process of establishing confidence in a PBPK platform to simulate a certain scenario, in a specific context, on the basis of scientific principles and ability to predict a large dataset of independent data thereby showing the platforms ability to predict a certain purpose. In the context of PBPK models, qualification is purpose and platform version specific.

Sensitivity analysis: Quantitative evaluation of how changes (e.g. due to uncertainty or variability) in input parameters influence the model output.

System dependent components: Parameters related to human physiology (in the population simulated) e.g. anatomical representation, organ blood flow, tissue composition, abundance of enzymes and transporters.

Uncertainty: A lack of certainty/confidence about the value of a parameter or the physiological processes due to either incomplete data or to an incomplete understanding of a process. Uncertainty can often be reduced by collecting more and better characterised data. Uncertainty can be qualitative or quantitative.

Verification: Model verification is part of the qualification focused on the assessment of the correctness of the mathematical model structure including details of the differential equations used and the parameterisations of the model.

Pharmacokinetic parameters used

AUC: Area under the plasma/serum concentration-time curve

CL: Clearance

CL_{int}: Clearance intrinsic

CL_H: Hepatic clearance

C_{max}: Maximum /peak concentration

C_{min} Minimum concentration

f_m: Clearance fraction via metabolic pathways

f_u: Fraction unbound in plasma

f_{ugut}: Fraction unbound in gut (entrocytes)

f_{umic}: Fraction unbound in microsomes

K_a: Absorption rate constant

K_{deg}: Degradation rate constant

K_i: Inhibition constant

K_{inact}: Rate of enzyme inactivation

K_m: Michaelis constant

$t_{1/2}$: Elimination half-life

t_{max}: Time to reach Cmax

V_{max}: Maximal initial metabolism/conversion rate

Appendix 1: Qualification of the PBPK platform

To certify that a PBPK platform can be used for an intended regulatory purpose, the ability of the platform to perform that specific type of simulation should be evaluated and in some cases, this requires that the PBPK platform should be qualified for the intended purpose. The extent of qualification required depends on the regulatory impact of the modelling (see below).

The qualification could also be assessed within the context of a regulatory submission. However, a qualification issued within the context of a particular regulatory submission should be considered only valid for that particular submission and would need to be resubmitted and re-evaluated in future applications.

Qualification of a PBPK platform for an intended purpose may occur via a CHMP qualification procedure (EMA/CHMP/SAWP/72894/2008/Rev.3). If there is a CHMP qualification opinion supporting the intended use of the platform, then the qualification is presented on the European Medicines Agency's (EMA) web site and a reference to this location in a regulatory submission is sufficient. In this case, the qualification can be referred to in future applications with the same intended use.

Qualification can include published papers if the included validation dataset is sufficiently current and described in sufficient detail to allow a thorough understanding of the data by regulators. When the PBPK platform is used in a regulatory submission related to a certain medicinal product, the predictive performance of the drug-specific model needs to be evaluated (see Appendix 2).

'in case of doubt on the relevance or the robustness of available system data included in the platform, particularly if used for high regulatory impact simulations, the applicant is strongly encouraged to seek CHMP Scientific Advice for further guidance.

Qualification of the PBPK platform for the intended purpose

In general, to qualify the system model of a PBPK platform, compounds with similar ADME characteristics to that of the intended use should be included in a pre-specified data set. For each drug compound, *in vivo* and *in vitro* data relevant for the intended use should be supplied in a table form. The dataset should, if possible, cover a range of pharmacokinetic characteristics that could influence the outcome. A restricted dataset could in some cases lead to constraints in the applicability of the qualification. The number of drug compounds included in the dataset and the range of pharmacokinetic properties covered by the dataset will affect the confidence in the PBPK platform and what it may be qualified for. It is recognised that the qualification dataset is data, and application, specific and therefore needs to be justified in each case. It is considered that e.g. eight to ten compounds is indicative of a sufficient number. If possible, it should be ensured that there are additional drugs included in the qualification set that were not used in the platform building.

In general terms, the qualification report for a particular purpose of use should show the ability of the PBPK platform to predict observed outcomes. The search strategy for the in vivo studies included to support the intended use of the PBPK platform should be shown and justified. Any references that are cited to support the qualification should be discussed and provided as supporting documents. The determination of adequacy of the simulations will be assessed on a case-by-case basis taking consideration the variability of clinical data and the impact of the modelling.

Qualification requirements at different levels of regulatory impact

When determining the level of qualification needed, the regulatory impact of the modelling should be considered. The regulatory impact is directly linked to the risk to the patient in case the modelling

predictions or assumptions lead to erroneous regulatory decisions. The impact of a simulation also depends on how much weight of evidence the PBPK simulation will have in a certain scenario (i.e., how much other data are available to support a certain decision), the therapeutic context and the resulting treatment recommendations. Regulatory impact can be classified as high, moderate and low[2] and the higher the impact, the greater the requirements on qualification of the PBPK platform. Different impact levels and the associated requirements are illustrated below. The level of regulatory impact should be discussed and justified in the submission.

High regulatory impact analyses

Simulations that are the key source of information to be included in the SmPC are generally considered a high-impact analysis. Whether situations should be considered high impact also depends on the availability of supportive data and on the therapeutic context. High impact simulations could include but are not limited to:

- the use of a PBPK model in place of clinical data (e.g. to waive interaction studies, to simulate non-studied scenarios);
- evaluation of the investigational drug as a victim of DDIs in a pharmacogenetic subpopulation, or in paediatric patients;
- evaluation of complex DDIs where e.g. the combined effect of two inhibitors are simulated;
- prediction of drug-drug interaction assessing other posologies compared to an available DDI study;

To decide if an intended use can be established for high regulatory impact decisions, considerations need to be given as to whether the science is mature enough. This would include valid system data (including abundance data if relevant) and demonstrated *in vitro-in vivo* correlations. It could also include demonstrating the interplay between physiology and the drug substance /drug product.

Examples to illustrate the concept of qualification for high impact situations are described below. A similar concept should be applied to other high impact analyses.

Example 1: Qualification of the ability to quantify the effects on investigational drugs being victim of drug interaction

To qualify the PBPK platform to quantitatively predict the effect of inhibition of an enzyme on the pharmacokinetics of drugs metabolised by the enzyme, adequate prediction of observed *in vivo* effects of inhibition of the enzyme in question should be demonstrated. This should be made using a pre-specified qualification dataset and should include simulation of inhibition effects on drug exposure and derived pharmacokinetic parameters such as total clearance, clearance through each pathway, bioavailability, AUC, C_{max}, $t_{1/2}$ etc. If the Applicant wants to qualify the platform for inhibition processes that are time-dependent, additional parameters should be simulated, such as time to steady state.

The qualification dataset should, if possible, consist of a series of drug substances (victims) eliminated to a significant extent through metabolism catalysed by the enzyme in question. For each drug, *in vivo* data supporting the clearance fraction of the pathway/contribution of the enzyme (f_m) should be presented. Preferably, the chosen drug substances should reflect different degrees of dependence of clearance on blood flow, plasma protein binding and, if relevant, different degrees of intestinal first-pass metabolism.

[2] Manolis E, Rohou S, Hemmings R, Salmonson T, Karlsson M, Milligan PA. The Role of Modeling and Simulation in Development and Registration of Medicinal Products: Output from the EFPIA/EMA Modeling and Simulation Workshop. *CPT: Pharmacometrics & Systems Pharmacology*. 2013;2(2):e31-. doi:10.1038/psp.2013.7.

The predictive performance of the used inhibitor files included in the qualification should be demonstrated. In case there are a limited number of inhibitors of the specific pathway and *in vivo* data on inhibition is scarce, the qualification could also be made using data on the consequences of genetic polymorphisms in the enzyme in question.

Example 2: Qualification of the ability to detect investigational drugs as perpetrators of drug interaction

The PBPK platform should be qualified to predict whether an investigational drug may act as a perpetrator in drug interactions *in vivo*. The concept is described for competitive enzyme inhibition, but can be applied also for other interaction mechanisms.

The qualification should aim at showing the capacity to detect the observed *in vivo* inhibitory effect of different inhibitors on sensitive probe substrate(s) for the enzyme in question and the ability to quantitatively predict available *in vivo* DDI study results need to be shown. The qualification dataset should be pre-specified and should include inhibitors of different potency. The predictive performance of the probe substrate PBPK model included in the qualification should be demonstrated (see appendix 2). Furthermore, the f_m of the substrate should be confirmed by *in vivo* data, e.g. from a study with a selective strong inhibitor of the enzyme or from a study in a genetic sub-population having a markedly reduced activity of the enzyme. Non-clinical data may only be used for f_m estimation e.g. at an early stage of model development or for a low impact example.

If the enzyme, such as CYP3A4, is expressed at multiple sites, accurate prediction of inhibition at each site should be demonstrated using data for probe drugs with well characterised interactions at each site and with focus on PK parameters (e.g. C_{max}, AUC), where data exists. The inhibition at the site of the enzyme over time should be discussed, if this were for a CYP3A substrate, it would it be considered adequate to separate the intestinal and hepatic contributions via differential effects on C_{max} vs $t_{1/2}$.

Qualitatively, false negatives, i.e. incorrect rejection of a drug in the qualification dataset as perpetrator, should be addressed, e.g. by considering whether sensitivity analysis could be applied to detect the *in vivo* perpetrator potential.

The qualification will only be valid for situations covered by the qualification dataset, e.g. only for the specific enzyme(s), site of inhibition (e.g., liver, intestine) and the type of background data (including pharmacokinetic data, the system parameters and the population used) on which the simulations were based.

Example 3: Simulation of exposure in paediatric population

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, or no, clinical exposure data and heavily rely on PBPK modelling are considered to be of high regulatory impact applications.

In the case of PBPK modelling without clinical PK data in the target age range, the platform qualification needs to meet strict qualification requirements including predictive performance of the model for a large number of compounds with similar ADME properties in the same population.

Example 4: Biopharmaceutical application- particle size specification

To qualify a model for biopharmaceutical applications e.g. to define product specifications for particle size in the absence of any clinical data, it should be demonstrated that the effect of particle size versus dissolution and PK exposure (AUC and C_{max}) is captured by the model for a number of drugs with similar physicochemical and biopharmaceutical properties and over a similar range of particle sizes.

Moderate and low level regulatory impact analyses

For situations that are not considered of high regulatory impact analyses, as previously outlined, the applicant should justify if a particular situation may be considered of moderate or low level impact and a model should be qualified accordingly e.g. when PBPK is used to gain mechanistic understanding in a clinical development programme and trials will ultimately include PK sampling to fully characterise the PK, this may be justified as low impact and no formal PBPK platform qualification is needed. Similarly, when PBPK is used to support the dose selection for a study in a specific paediatric population and full or limited confirmatory PK data is available this can be argued to be of low or moderate impact.

When sparse PK data are available in the particular age range, the platform qualification could consist of demonstration of predictions of the pharmacokinetics of drugs with similar ADME properties as the investigational drug, such as having the same major elimination pathways. As a guide, a minimum of two compounds with similar ADME properties as the new investigational drug and with PK data in the particular age range is proposed.

When qualifying a PBPK platform intended for paediatric dose selection e.g. in a Paediatric Investigational Plan (PIP), the system data and parameters accounting for the impact of body size, maturation and other potential co-variates affecting the model predictions need to be specifically presented and justified.

Compound files supplied in the PBPK platform

The predictive performance of any compound files (e.g. inhibitors, inducers and probe drugs) used in a simulation needs to be confirmed. This could be done in a qualification procedure for an intended purpose of the PBPK platform or in a regulatory submission (section 1).

To support that a compound file can be used for simulation, the simulated pharmacokinetics of the specific drug included in the file should be compared against several representative *in vivo* pharmacokinetic studies for this drug. The data to be supplied includes AUC, C_{max}, $t_{1/2}$ and the plasma concentration-time course including the shape (both linear and semi-log graphs).

If deemed necessary for the specific application, the compound files included in a commercial PBPK platform can be modified, but the modifications need to be clearly described and justified. The consequences for the validity of qualification(s) referred to needs to be supported. Some re-qualification may be needed.

Differences between PBPK platform versions should be clearly stated in the report and discussed. If a given version of a platform has previously been considered qualified for a certain use, the possibility to extrapolate the qualification from the previous version to the updated new version(s) should be justified if the new version is to be used for a regulatory purpose.

Verification

A part of the qualification is focused on the correctness of the mathematical model structure (verification). Details of the differential equations used and the parameterisations of the PBPK model needs to be presented. The maintenance of mass-balance as well as blood flow balances within the model should be supported. It should be ensured that there are no numerical errors. If the PBPK platform has gone through a CHMP qualification procedure for an intended purpose, it is assumed that the verification is satisfactory for the parts of the platform used for this purpose. In other cases, the verification approach that has been used to support the PBPK platform as well as the verification results should be available on request.

Appendix 2: Evaluation of the predictive performance of the drug model

The PBPK report should include an evaluation of the investigational drug PBPK model, to ensure that the drug model consistently describes the observed pharmacokinetic behaviour of the drug.

The evaluation should be made by assessing the ability of the model to predict the range of the observed outcome of representative *in vivo* pharmacokinetic studies or population pharmacokinetic analyses, e.g. different dose levels and single and repeated drug administrations. Simulations should be performed in the population of interest and for a large number of individuals (>100) is recommended. Additional support could be gained by simulating potential dose dependency (non-linearity), drug interactions different routes of administration (e.g. intravenous v's. oral) and urine excretion. A critical discussion of the representativeness of the selected studies should be included. PK data from a 'related' preclinical PBPK model may be included as supportive.

The comparison of the simulated and the observed plasma concentration-time data should be presented as plots, such as simulated vs. observed data using linear and semi-log plots and as tabulations. Observed individual data should be used for comparison. Visual predictive plots should be presented comparing the central trend and variability of the observed data with the simulation (both log and linear scale including observed percentiles (i.e. 5th and 95th) of the observations and the simulation-based confidence intervals (i.e. 95%) around the observed percentile). The consequences of poor prediction in any part of the plasma concentration time curve should be discussed and justified (C_{max}, t_{max}, $t_{1/2}$ and AUC). The evaluation of the drug model for a certain purpose should focus on evaluating the parts of the drug model that are central to the intended purpose.

The acceptance criteria (adequacy of prediction) for the closeness of the comparison of simulated and observed data depends on the regulatory impact and needs to be considered separately for each application. The consequences of poor prediction should be discussed and justified, e.g. the acceptance limits for a victim drug must be set in perspective of the concentration-effect and concentration-safety relationships of the drug at the time of submission. Biologically plausible reasons for any discrepancy in the prediction should also be considered.

Examples of the evaluation of drug models in various scenarios are described as follows:

Example 1: Evaluation of the drug model when the investigational drug is a victim drug

When the investigational drug is a victim of a DDI, the prediction of basic *in vivo* pharmacokinetic data should be presented. If the interaction is mediated via a metabolic enzyme, predictions of the results from an *in vivo* drug-interaction study with a known strong inhibitor of that enzyme should be demonstrated to confirm the contribution of the metabolic pathway to the elimination of the drug. If a polymorphic enzyme is involved in the metabolism, adequate prediction of the results of a study on the effects of pharmacogenetics could be used to confirm the accuracy of the drug model.

When assessing the simulated results of the drug-drug interaction, it should be considered whether the inhibitor used in the study may affect other processes determining the disposition of the investigational drug (such as other metabolic enzymes and transport proteins). Also, if the enzyme mediating the interaction is significantly present in both the intestine and liver, it is important that the absorption of the investigational drug is well captured by the PBPK model and adequate prediction of effects on the investigational drug needs to be shown for inhibition at both locations with satisfactory prediction of C_{max} and $t_{1/2}$ as well as AUC.

Example 2: Evaluation of the drug model when the investigational drug is a perpetrator

For simulations aiming at qualitatively predicting the *in vivo* relevance of an observed *in vitro* enzyme inhibition by the investigational drug, it is important that the unbound concentration at the site of the enzyme is adequately simulated. This is supported by adequate prediction of the plasma concentration-time course for the investigational drug including relevant PK parameters such as AUC, C_{max} and $t_{1/2}$. If relevant, the possibility of transporter effects leading to higher hepatocyte than blood concentrations needs to be considered in the model (Guideline on investigation of drug interactions CPMP/EWP/560/95/Rev. 1). If the enzyme is present in the intestine, adequate prediction of the absorption of the investigational drug should be demonstrated.

Example 3: Simulation of exposure in an alternate population

When the investigational drug is to be simulated in a new population, the drug model evaluation should include demonstration of adequate prediction of the observed exposure in other populations; e.g., in paediatric applications, simulations of the pharmacokinetics in adults and other paediatric age groups can be used as supportive data.