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

Draft

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

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Executive summary

A growing number of regulatory submissions include Physiologically Based Pharmacokinetic (PBPK) models that require the use of specialised software platforms. If PBPK modelling is intended to support a regulatory decision, the PBPK platform needs to be qualified for the intended use and the predictive performance of the specific drug models needs to be evaluated. 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, to allow assessment of the predictive performance of the drug model. In addition, this document aims to clarify which supportive data are expected in order to qualify a PBPK platform for an intended purpose.

1. Introduction

For the purpose of this guideline, a PBPK model is defined as one that simulates the concentration of a drug over time in tissue (s) and blood, by taking into account the rate of its absorption into the body, distribution in tissues, metabolism and excretion (ADME) on the basis of interplay among critical physiological, physicochemical and biochemical determinants.. The majority of PBPK regulatory submissions today involve the use of commercially available specialised PBPK platforms. If used for regulatory decisions, simulations performed using these platforms need to be carefully assessed regarding e.g. ability of the platform to adequately perform simulation of the intended type, as well as drug model specific issues. These includes consequences of assumptions made, the validity and biological plausibility of input parameters, uncertainty around the determination or prediction of parameters, and clarity around any optimisation process or any update of the model based on *in vivo* data. The PBPK platform needs to be qualified for the intended use by showing adequately prediction of the same kind of situations with external data. Further, the predictive performance of the specific drug models needs to be evaluated. The level of these evaluations depends on how much weight of evidence the PBPK simulation will have in the decision making and the risk for the patient in case the modelling predictions or assumptions lead to erroneous regulatory decisions.

If PBPK modelling is used in the development of an investigational drug, it is strongly recommended that the *in vitro* and *in vivo* clinical pharmacology studies are designed to provide data to successively improve the model and support the planned model applications.

Presently, the main purposes of PBPK models in regulatory submissions are to qualitatively and quantitatively predict drug-drug interactions (DDIs) and 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 system knowledge is gained and confidence increases.

For the qualification of PBPK platforms for an intended purpose, sponsorsmay apply for a Committee for Medicines for Human Use (CHMP) qualification via its Scientific Advice (Qualification of novel methodologies for drug development: guidance to applicants EMA/CHMP/SAWP/72894/2008/Rev.3) or supply the qualification in the application where the PBPK modelling is applied. In the future qualification may also be supported by, e.g. learned societies. Seeking CHMP scientific advice for additional guidance on the use of PBPK modelling and simulation in support of regulatory submissions 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 on the conduct of clinical trials, 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).
- Pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev. 1).
- 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).
- A guideline on summary of product characteristics (SmPC) September 2009 (Eudralex vol. 2C).
- Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (EMEA/CHMP/89249/2004).
- Pharmacokinetic studies in man (Eudralex vol. 3C C3A).
- Guideline on reporting the results of population pharmacokinetic analyses (EMEA/CHMP/EWP/185990/2006).
- Note for Guidance on General Considerations for Clinical Trials (ICH E8, CPMP/ICH/291/95).
- Note for Guidance on Guideline for Good Clinical Practice (ICH E6, CPMP/ICH/135/95).
- Structure and Contents on Clinical Study Reports (ICH E3, CPMP/ICH/137/95).

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 a PBPK platform for an intended use. The guideline applies both to commercially available platforms and to in-house built platforms

Presently, the regulatory experience of PBPK involves primarily the drug-interaction area as described in the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr.*) and the Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009). PBPK modelling and simulation are also used to select paediatric and first in human dose. Specific examples on how to apply this guideline to other areas are not given. The guidance may, however, conceptually be applied when qualifying a PBPK platform for use in any area.

4. Qualification of the PBPK platform

To certify that a specific version of a PBPK platform can be used for an intended regulatory purpose, the ability of the platform to perform that specific type of simulation should always be explicit evaluated (i.e. the PBPK platform should be qualified for the intended purpose) using external data. The extent of qualification required depends on the regulatory impact of the modelling (see section 4.2).

A qualification of a certain version 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 (and version), 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 in future applications with the same intended use, and no new submission of the qualification data is needed.

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 need to be resubmitted and re-evaluated in future applications.

Qualification can include published papers if the included validation dataset is described in sufficient detail to allow a secondary assessment. In the future, qualification may also be supported by, e.g. learned societies. In these cases, their qualification report for a specific use of the PBPK platform should be submitted in the submission. The data set and results should be described in sufficient detail to allow a secondary assessment.

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. This is further described in Section 6.

If an in-house built computer program is used for high regulatory impact simulations (such as waiving of studies) the applicant is strongly encouraged to seek CHMP Scientific Advice for further guidance.

4.1. Qualification of the PBPK platform for the intended purpose

The process of qualification should be pre-specified. This should describe selection criteria for the drugs included in the qualification dataset and the *in vitro* and *in vivo* parameters for these drugs. The dataset should, if possible, cover a range of pharmacokinetic characteristics, such as permeability, extraction ratio, protein binding etc. that could influence the outcome. A restricted dataset could in some cases lead to constraints in the validity of the qualification. Any references describing the use of the PBPK platform that are cited to support the qualification (e.g., evaluations based on model drugs) should be discussed and provided as supporting documents.

The qualification report for a particular purpose of use should show the ability of the PBPK platform to predict observed outcomes, with adequate precision, for a wide variety of drugs based on certain types of background information (e.g. only *in vitro* data, or a combination of *in vitro* and *in vivo* data). For example, if the intended purpose is to predict whether a drug is an *in vivo* CYP3A4 inhibitor in adult healthy subjects, it needs to be shown that a wide range of weak to strong CYP3A4 inhibitors can be identified using the same set of background *in vitro* and *in vivo* information and having adult healthy subjects as the study population.

4.2. Qualification requirements at different levels of regulatory impact

When determining the level of qualification needed, the regulatory impact of the modelling should be considered. This can be classified as high, moderate and low (Manolis *et al* 2013) and the higher the impact, the greater the requirements on qualification of the PBPK platform. 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 recommendation (labelling). Different impact levels and the associated requirements are illustrated below. The level of regulatory impact should be discussed and justified in the submission.

4.2.1. High regulatory impact analyses

All simulations that affect the SmPC (Summary of Products Characteristics) are considered a high-impact analysis. This could include but are not limited to:

- the use of a PBPK model in place of clinical data (e.g. to waive studies, such as interaction studies, or to simulate non-studied scenarios);
- evaluation of the investigational drug as a victim of DDIs in a pharmacogenetic subpopulation (See Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products, EMA/CHMP/37646/2009) or in paediatric patients;
- evaluation of so called “complex DDIs” where e.g. the combined effect of two inhibitors are simulated (Investigation of drug interactions, CPMP/EWP/560/95/Rev. 1);
- prediction of changes of study design of an available DDI study, such as using other doses/dose regimens;

or

- simulations that are reflected in section 5.2 Pharmacokinetics information in the SmPC

As outlined above, whether these situations should be considered high impact also depends on the availability of supportive data and on the therapeutic context.

To illustrate the concept of qualification for high impact situations, two examples 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 ability of a PBPK platform to quantitatively predict the effect of inhibition of a specific enzyme on the pharmacokinetics of drugs metabolised by this 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 inhibition process is 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.

The predictive performance of the used inhibitor files included in the qualification should be demonstrated (see section 4.3). 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.

The scenarios that will be considered qualified will depend on the type of input data included in the qualification dataset. As an example, to qualify simulations of the effects of an inhibitor of a certain enzyme, *in vivo* data needs to be able to support the f_m of the pathway/contribution of the enzyme to the elimination of the drugs in the qualification dataset. If the results of *in vivo* DDI studies with a potent inhibitor have been used to support f_m, this will be considered the qualified scenario. If mass-balance data are used together with *in vitro* data on metabolite formation, the qualification will be valid for this specific input data scenario.

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

This section describes how 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. The qualification dataset should be pre-specified and should include a large number of inhibitors of different potency. If the number of known *in vivo* inhibitors of the enzyme in question is limited, an attempt should be made to include all known inhibitors. The predictive performance of the probe substrate PBPK model included in the qualification should be demonstrated (see section 4.3).

When aiming to predict the ability of a drug to act as perpetrator of drug interactions 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.

Again, 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.

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.

4.3. Compound files supplied in the PBPK platform

The quantitative 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 qualification procedure for an intended purpose of the PBPK platform or in a regulatory submission.

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, Cmax, t1/2 and the plasma concentration-time course including the shape (both linear and semi-log graphs).

For example, for an inhibitor compound file the ability to quantitatively predict results of available *in vivo* DDI studies with probe substrates of the inhibited enzyme needs to be shown in addition to the basic pharmacokinetic results. If the enzyme is expressed at multiple sites, such as CYP3A4, accurate prediction of inhibition at each site should be demonstrated. The inhibition at the site of the enzyme over time should be discussed and supported by suitable parameters.

Also for a substrate compound file, the ability to quantitatively predict available *in vivo* DDI study results need to be shown. Furthermore, the f_m of the substrate should be confirmed by *in vivo* data, e.g., from a study with a strong inhibitor of the enzyme or from a study in a genetic sub-population having a markedly reduced activity of the enzyme. Data should support detection of inhibition at each site of the enzyme.

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. A new qualification may be needed.

4.4. Version control of the PBPK platform

Many commercial PBPK platforms are regularly updated, therefore changing the mathematical models, drug specific parameters for model drugs or physiological parameters for different populations. While it is understood and encouraged that PBPK platforms evolve with new science and published data, it introduces the need to demonstrate that a previously performed qualification is valid also for the new version.

Differences between PBPK platform versions should be clearly communicated and thoroughly discussed. If a given version of a platform has previously been considered qualified for a certain use, the possibility to extrapolate the predictive performance from the previous version to the updated new version(s) should be supported if the new version is to be used for a regulatory purpose (See section 4.2).

If the version of a platform used in a submitted report is not the most recent one, the Applicant should discuss whether the simulation would have been significantly different if the most recent version had been used.

4.5. Verification

The model verification is a part of the qualification focused on the correctness of the mathematical model structure. Details of the differential equations used (the mathematical model) 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; equations and parameter values should be devoid of syntax or mathematical errors. Furthermore, it should be ensured that there are no numerical errors (World Health Organisation, 2010). 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.

4.6. Physiological parameters for populations included in the PBPK platform

The system-dependent parameters, including typical physiological parameters for the population(s) for which qualification is claimed, should be presented and justified. The data should be presented in an appendix to the qualification report in a structured way to allow assessment. If possible, literature references should be provided as full articles and the rationale for the chosen system-dependent parameters should be given.

If the PBPK platform has gone through a CHMP qualification procedure for an intended purpose, it is assumed that the qualification for the involved physiological parameters is satisfactory.

4.7. Installation control of the PBPK platform

A control of the installation of the PBPK platform should be performed to ensure that the program and any new versions work fully as intended when installed in the computing environment. The key functionality of the program should be tested. The qualification report should include a presentation of how this was done. The installation processes should be included in a CHMP qualification procedure.

5. Reporting of PBPK modelling and simulation

This part of the guideline describes the recommended content of a PBPK report and issues that should be addressed in order to enable assessment by regulators.

It is not necessary to append documents to the report that are already included in other parts of the dossier (e.g., study reports, analytical reports etc.). However, cross-references with hyperlinks should be provided to allow easy navigation.

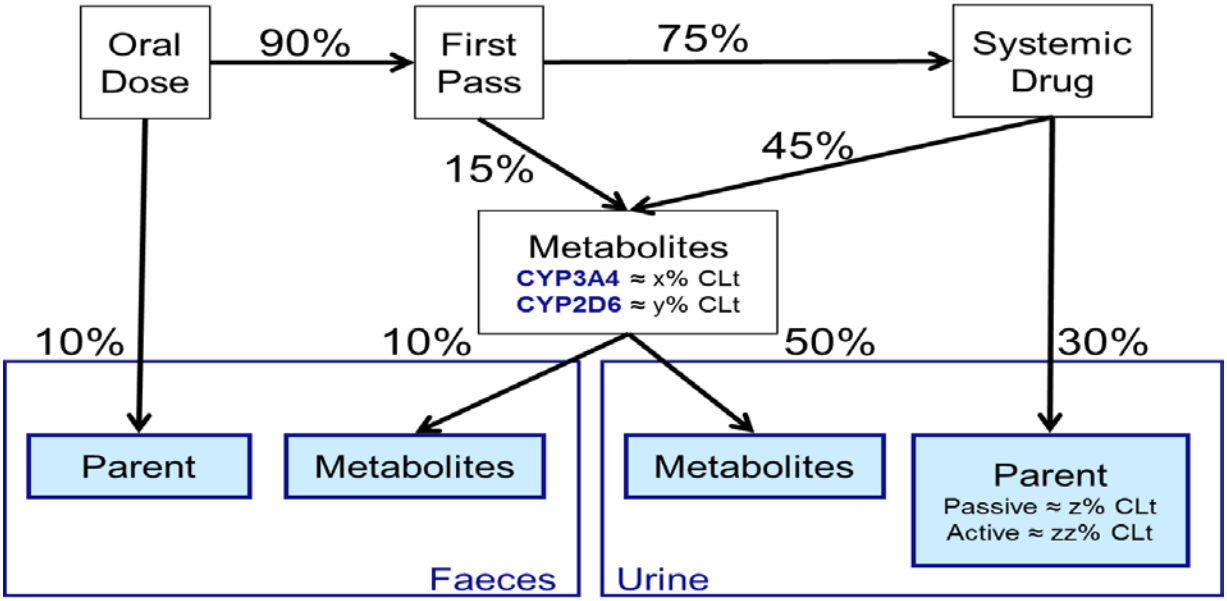
5.1. Objective and regulatory purpose

The objective and the intended regulatory purpose of the PBPK modelling, including any proposed changes to the SmPC, should be clearly described at the start of the report.

5.2. Background information

The introduction of a PBPK report should include information about the investigational drug, emphasising *in vivo* and *in vitro* ADME and other relevant pharmacokinetic characteristics of the drug (see section 5.5). If possible, a quantitative mass-balance diagram (Figure 2) presenting elimination pathways with involved enzymes and transporters, should be included along with an explanatory text and references.

Figure 2: Example of a quantitative mass balance diagram after oral and intravenous 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 (Shepard et al 2015).



Additional information of relevance for the PBPK model could include data on solubility, permeability, potential dose- or time-dependent pharmacokinetics, DDIs or effects due to pharmacogenetic differences. The appropriateness of the used population should be justified.

The report should also include sufficient background information to place the PBPK modelling in its context in the clinical development of the drug. If the PBPK modelling is used to predict scenarios where the exposure to the investigational drug may be altered, 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 exposure (a range for relevant exposure parameters specifying what change in exposure would justify a posology adjustment) should be defined.

If simulating pharmacokinetics in paediatric patients, an overview of the available pharmacokinetic information in other age groups, such as older children and adults, should be presented as a background for the discussion of the confidence in paediatric PBPK model predictions and the consequence of variability and uncertainty. Available PBPK simulations of pharmacokinetics in adults should be submitted as support. Effects of maturation, such as potential quantitative changes in the contributions of the various elimination pathways in paediatric age subsets should be addressed.

5.3. Assumptions

An explicit and systematic discussion of the assumptions made in the submitted drug model and in the associated analysis should be provided. Data to support the assumptions and their biological plausibility should be presented and discussed as well as the impact the assumptions have on the model and the outcome.

Unless well-established or impossible, the effects of assumptions should be tested in additional experiments or simulations. A discussion of which of the assumptions are considered testable should be provided. Some assumptions may be tested through sensitivity analysis (see section 5.5.4). The approaches used to test the assumptions and the outcomes should be presented.

5.4. System dependent parameters

The parameters of the simulated datasets should be summarised. Any modification of the default values of the system-dependent parameters supplied in a commercial PBPK platform should be justified e.g., changing the values of the degradation constant (kdeg) of metabolising enzymes (Investigation of drug interactions, CPMP/EWP/560/95/Rev. 1). A re-qualification may be needed, see section 4.4. The ontogeny of enzymes for paediatric modelling could be justified by using a conservative approach supported by literature references.

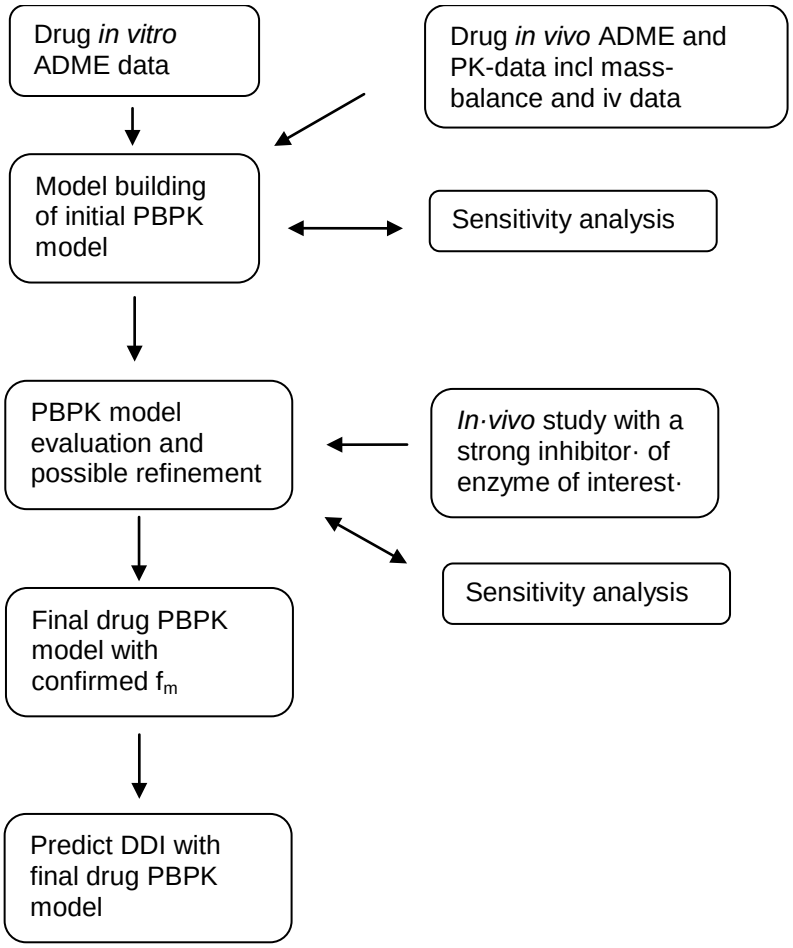
5.5. Drug model

The PBPK report should include a thorough description of the investigational drug model. The different components of the drug model development that should be addressed in the report are described in detail below.

5.5.1. Description of model building

The building of a PBPK model is a continuous process that includes construction, verification, evaluation and modification of the model prior to its application. A description of the full history of the construction of the PBPK model through discovery and development is not needed. However, an overview of the model building should be supplied, with more detailed information on the supportive data for important assumptions and on uncertain parts of the model. Any adaptation of the model to optimize the fit of the simulation to *in vivo* results should be justified, and it should be clear during which part of the construction process the adaptation was performed. If several updates were made to adapt the model to improve the fit for a certain parameter, the consequences of the choices made for the subsequent simulations should be discussed. The overview can be illustrated with a figure (Figure 3).

385 **Figure 3: Example of a modelling workflow**



386

387 5.5.2. Drug dependent parameters

388 A summary of parameter name, parameter values (mean with known or predicted variability) and
389 sources of the parameter values, ideally compiled in table format (Appendix 1, Table 1), should be
390 included in the report. The parameters described should include physico-chemical properties and ADME
391 data. If there is more than one source of a certain parameter, the value chosen should be justified and
392 the consequences discussed.

393 Some parameters in the model can be either measured or predicted (e.g. fumic, log D). Importance for
394 the model of such parameters should be assessed. If deemed important, the parameters should
395 preferably be measured or otherwise justified.

396 For estimated parameters, the chosen estimation procedure must be described such as the used
397 objective function, minimisation method and error models. The estimated parameter value should also
398 be discussed with regard to its biological plausibility.

399 Consideration should be given to whether there are parameters in the model that are correlated and if
400 there is uncertainty in the value of more than one of the parameters. In the case that an identifiability
401 issue is suspected additional *in vitro* or clinical data may be required to increase certainty in the
402 parameters. A description on how any identifiability issues have been handled should be given.

5.5.3. Drug model structure

The model structure, including the absorption model for orally administered drugs, should be described in the report. The scientific rationale for using the specific model structures should be provided, together with assumptions associated with the model. If lumping of compartments is made this should be justified and potential consequences should be discussed.

5.5.4. Sensitivity analysis

Sensitivity analysis can broadly be described as a systematic investigation that leads to an understanding of how changes in the model input parameters (both system and drug dependent parameters) can influence the simulation outputs.

The approach for sensitivity analysis and the range of the parameter values tested in the sensitivity analysis should be described in the analysis plan. The range of parameter values should be justified based on prior scientific knowledge or known variability in the estimation, and a conservative approach is recommended. The basis for the decision to go forward with as specific value of a parameter should be presented.

Sensitivity analysis should be performed for all parameters that are likely to markedly influence the outcome of the simulated pharmacokinetics and/or the model application. This includes key experimentally determined parameters (such as Ki), parameters with a variety of values reported in the literature (such as kdeg) and parameters that are difficult to determine, such as accumulation within hepatocytes or fu in enterocytes. Important assumptions (see section 5.3) can be subject to sensitivity analysis using a “worst-case” approach. Parameter values that are highly uncertain should be used with caution.

When the sensitivity analysis is performed in the modelling of the investigational drug as perpetrator of DDIs, the PBPK model of the investigational drug needs to maintain its ability to predict the observed plasma concentration-time curve of the perpetrator drug. The consequence of the uncertainty in an important parameter for the prediction could therefore be added to the uncertainty in the interaction parameters (e.g. K_i) by performing sensitivity analyses on these parameters (Investigation of drug interactions, CPMP/EWP/560/95/Rev. 1).

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.

5.5.5. Characterizing the level of confidence in PBPK models, including uncertainty

The reliability of the evaluated model predictions should be addressed. Uncertainty reflects a lack of knowledge about the true value of a parameter or the validity of an important assumption. In principle, uncertainty can be reduced e.g. by more precise measurements. The uncertainty could also be addressed by sensitivity analyses for specific input parameters, as described above, or by additional experiments to get a better understanding of the uncertain parameter. The best way to handle uncertainty in a model besides these measures is presently not clear. The applicant is encouraged to follow the scientific literature in this area and to seek CHMP Scientific Advice as appropriate.

5.5.6. Evaluation of the drug model

A drug model must be shown to be capable of predicting the observed basic pharmacokinetics of the investigational drug before the model can be used for simulations of special situations. Otherwise it is necessary to refine and update the model with more ADME data. The PBPK report should include an evaluation of the predictive performance of the investigational drug 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 outcome of representative *in vivo* pharmacokinetic studies or population pharmacokinetic analyses, preferably at different dose levels and at single and repeated drug administrations. Additional support could be gained by simulating potential dose dependency (non-linearity), DDIs, different routes of administration (e.g. intravenous vs. oral) and urine excretion. A critical discussion of the representativeness of the selected studies should be included.

The comparison of the simulated and the observed plasma concentration-time data should be presented as plots of simulated against observed data (linear and semi-log plots) and as tabulated pharmacokinetic data. Visual predictive plots may be presented comparing the central trend and variability of the observed data with the simulation. The consequences of poor predictive performance in any part of the plasma concentration time curve should be discussed (C_{max}, t_{max}, $t_{1/2}$ and AUC).

Any outliers in observed pharmacokinetic data should be addressed and the potential reasons for the outlying data should be discussed.

The acceptance criteria for the closeness of the comparison of simulated and observed data need to be considered separately for each situation 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. Biologically plausible reasons for any discrepancy in the prediction should also be considered.

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. For example, for a high regulatory impact simulation of a drug as victim of a DDI involving a certain enzyme, the drug model evaluation may include demonstration of adequate prediction of the observed results of an *in vivo* drug-interaction study with a well characterised inhibitor of the same enzyme, in addition to prediction of basic *in vivo* pharmacokinetic data. If the affected enzyme is significantly present in several tissues, such as CYP3A in the intestine and liver, 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. 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 results of the simulation if the inhibitor used in the study may have affected other proteins involved in the disposition of the investigational drug should be considered. For high impact simulations aiming at qualitatively predicting the *in vivo* relevance of an observed *in vitro* enzyme inhibition by the investigational drug, the most important part of the simulation is that adequate unbound concentration is simulated at the site of the enzyme. This is supported by demonstration of an adequate prediction of the plasma concentration-time course for the investigational drug. However, the possibility of transporter effects leading to higher hepatocyte than blood concentrations needs to be considered in the simulation (See Section 5.5.4 and 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.

5.6. Results

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

The details of all simulation conditions should be specified including, but not limited to, dosing information, number of individuals, length of study, etc.

The 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 separately in an executable format.

The outcome of performed sensitivity analysis should be provided (see section 5.5.4).

5.7. Discussion of the simulation results and regulatory consequences

The contribution of the PBPK modelling and simulations to regulatory decision making and the regulatory impact (high, moderate or low) should be explicitly stated.

Any decision (e.g., on dose adjustments) based on PBPK modelling of changes in the exposure to the investigational drug should consider the relationship between exposure and efficacy/safety, taking into account the exposure target range, if identified (see section 5.2).

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 decision making.

A discussion of the scientific plausibility of the simulation results should be provided taking into account data from other sources.

Definitions

The following terms and definitions will be used for the purpose of in this guideline:

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

Drug dependent 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 , number of distribution compartments, etc.) and connecting organ blood flows.

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 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 and uncertainty in input parameters influence the model output.

System dependent components: These include 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 knowledge about the true value of a parameter or the true physiological processes. This occurs due to a lack of knowledge either from incomplete data or an incomplete understanding of a process. Uncertainty can often be reduced by collecting more and better data. Uncertainty can be qualitative or quantitative

ADME: Absorption, distribution, metabolism and excretion

AUC: Area under the plasma concentration-time curve

CHMP: Committee for Medicines for Human Use

CL: Clearance

CL_{int}: Clearance intrinsic

CL_H: Hepatic clearance

C_{max}: Maximum /peak concentration

C_{min} Minimum concentration

DDI: Drug-drug interaction

EMA: European Medicines Agency

f_m: Clearance fraction via a certain metabolic pathway

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_m: Michaelis constant

PBPK: Physiologically Based Pharmacokinetic models

PIP: Paediatric Investigational Plan

SmPC: Summary of product characteristics

$t_{1/2}$: Half-life

t_{max}: Time to reach Cmax

V_{max}: Maximal initial metabolism rate

References

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APPENDIX I

Table 1: Example of drug-specific information needed for a parameter during PBPK model development of a candidate drug

Parameter	Mean ±SD / or min-max)	Reason for use	Source
Parameter 1			
Parameter 2			
Parameter 3			
etc			