EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/59169/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation' (EMA/CHMP/458101/2016)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	UCB
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3	Alicia Paini (European Commission - Joint Research Centre)
4	International Consortium for Innovation and Quality in Pharmaceutical Development
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6	SIMCYP LTD
7	Astellas Pharma Europe BV
8	Critical Path Institute (C-Path)
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10	EFPIA
11	Medicines Evaluation Board (the Netherlands)
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1. General comments – overview

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1	The guideline is mainly focused on DDI and paediatric dosing, but it would be useful to integrate other applications of PBPK modelling as Mechanistic Absorption Modelling. When discussing about qualification it would be helpful to make the difference between drug dependent parameters and physiological/biochemical/structural parameters. The guideline proposes 3 different ways for the qualification: (a) CHMP qualification, (b) qualification in the application and (c) qualification by learned societies. The 1st one concerns the vendors, the 2nd one concerns the sponsor and the 3rd one we do not know. Clarifications would be helpful as the vendors could "easily" qualify the physiological/biochemical/structural parameters whereas the sponsors could focus on drug dependent parameters and modelling. We are concerned by the number of compounds/studies recommended or requested to qualify the PBPK modelling for an intended purposes. In different areas there are only a few number of data sets or published cases available. But combined with a strong scientific rational it can be really valuable to support results of PBPK modelling and simulations. For many years, PBPK modelling is used to define safety thresholds in the environment area on the basis of (fortunately) a few number of case studies and strong scientific rationales. At some point, the draft guideline suggests that IV data is mandatory for the PBPK model building. There are examples of drug development for which IV administration is not needed (or even possible). But it does not mean that a trustable PBPK model cannot be built on the basis of oral data only. The draft guideline suggests use the very last version of the PBPK platform	The comment contains a series of specific comments which have been addressed in the text in the relevant sections. Of note the focus of the guideline is in line with the experience of EMA to date in terms of models that have been submitted to support regulatory decision making. A statement is included in the final guideline that *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*. Additional information on biopharma examples has been added. IV data is not mandatory but its usefulness is recognised. Any version of the software, if appropriately qualified, is accepted.

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	"to discuss whether the simulation would have been significantly different if the most recent version had been used". It will request a huge amount of work to do so for the sponsor and might discourage them from including PBPK modelling in their submissions. It would be better to consider as valid PBPK modelling performed in an "old" qualified PBPK platform.	
2	1. Clarify adequate clinical data for parameter optimization/ estimation as in some cases plasma is not informative (e.g., some transporter parameters). Clarification on this links to sensitivity analysis and understanding of the rate limiting process. 2. Consider also use of integrated population PBPK approach within Bayesian framework to estimate parameters associated with high uncertainty (L438) 3. Important to report error in parameter estimates, not just biological plausibility (L398) 4. Overall bias of the guideline towards simpler scenarios (mDDI, CYP3A4). Some guidance/recommendations for complex scenarios involving multiple mechanisms/ metabolism-transporter DDIs/ sequential processes/prediction of tissue profiles is needed	The comment contains a series of specific comments which have been addressed in the text in the relevant sections. Of note the focus of the guideline is in line with the experience of EMA to date in terms of models that have been submitted to support regulatory decision making. A statement is included in the final guideline that *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*.
3	This document is a step forward in promoting the use of PBPK models in regulatory submission. The document describes well the information needed to evaluate and document these models. A suggestion would be to provide in the appendix a reporting template exclusively to be used to report PBPK models and applications/analysis. This will allow to report in a harmonized and organized way the PBPK models and analysis, that then can be submitted, the template should allow a degree of freedom in what to report. If possible to add in appendix a standardized template to report PBPK models (see Ciffroy et al., 2016). Another reporting template, in Excel format, has been developed by the JRC for the reporting of PBK (PBPK) and other compartment-based models. This can be made available upon	The utility of a template for reporting is acknowledged and it is anticipated said will be developed in due course.

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	request.	
4	The guidance is almost only about DDI and pediatric PBPK applications and this makes the relevance to other areas unclear. We are concerned that the use of a very limited number of examples limited to these 2 areas may lead sponsors to be too cautious in their submission of applications of PBPK modelling beyond these 2 areas. There is very little mention of absorption modeling – which seems to suggest that confidence in absorption modelling is currently low although this was not the situation reported by an IQ working group where BCS1 molecules were associated with highly confident predictions (reported in Jones et al. CPT 2015, 97(3)). In particular, many sponsors would appreciate more detailed guidance on the EMA view of absorption modelling for food effect or PPI related drug interactions. Also, to enable the guidance to be applicable to scientific advances in PBPK in the near future we recommend an additional paragraph to encourage application of PBPK to areas beyond the well-known examples of metabolic CYP-based DDI. For example the following might also be considered: mechanistic absorption modelling, hepatic or renal impairment, multiple dose prediction from single dose data, support justifications for proposed commercial products involving complex aspects e.g. with regard to poor solubility, solid state transitions, advanced drug delivery etc. We feel that in cases of clear CYP3A induction without confounding TDI the modeling has been verified and published. (e.g. Xu et al., 2011 Drug Metab. Dispos. 39, 1139-48. Einolf et al. (2014). Clin Pharmacol Ther 95(2): 179-188 and most recently Wagner et al. Clin Pharmacokinet. 2016 Apr;55(4):475-83. However, there is little mention of PBPK modeling of enzyme induction in the guidance and we suggest clarifying the EMA view on when PBPK and IVIVE for induction can be used.	The comment contains a series of specific comments which have been addressed in the text in the relevant sections. The focus of the guideline is in line with the experience of EMA to date in terms of models that have been submitted to support regulatory decision making. Details have been included e.g. *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*.

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	The overall document seems to imply that IV data is mandatory for PBPK model construction. We feel that this can strongly limit the use of PBPK particularly at earlier stages of development and there are cases where non-clinical and clinical oral data can be sufficient without need for IV data. We suggest clarifying the EMA view on IV data requirements. Currently the guidance uses terms which are quite influenced by the SimCYP platform (e.g. "compound file", "population file" etc.) please consider a more software neutral presentation so that those not familiar with SimCYP can also understand well. Perhaps further definitions could be added? When discussing qualification within the document, a clearer separation of the drug dependent & drug independent components would be helpful. Particularly when considering implementation of these practices and the roles of the software vendor versus the drug application sponsor a clearer separation of drug and system can be helpful. We are concerned about the potentially enormous efforts required to re-perform all submitted modelling in the latest software versions. This could become a major overhead and could thus limit the use of PBPK by sponsors. We feel that if a model in a particular version is deemed qualified then the model should remain qualified for its intended purpose irrespective of later software modifications. If the intention is to exclude old and obsolete platforms from submission, EMA should rather communicate that older versions are no longer qualified. This would be preferable to the requirements to have sponsors check using the latest released version.	
5	In analogy with paediatric population, PBPK models would be useful for predicting chemical disposition in older population as well incorporating	Accepted. If a PBPK platform is qualified, it can be used for prediction in older, or any alternate, populations.

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	individual variability conferred by genetic polymorphisms, health conditions, and physiological changes during aging. This aspect should preferably be addressed in the document. In that sense, I hereby refer to the Database for Physiologically Based Pharmacokinetic (PBPK) Modeling: Physiological Data for Healthy and Health-Impaired Elderly by Thomson C et al. (published in J Toxicol Environ Health B Crit Rev 2009; 12: 1-24.) In that database physiological parameter values were obtained from the peer-reviewed literature, evaluated, and entered into a database. Database records include values for important age-specific model inputs such as ventilation rates, organ volumes and blood flows, glomerular filtration rates, and other clearance-related processes. In total, 155 publications comprising 1051 data records for healthy older people were included and 115 data records for older people with conditions such as chronic obstructive pulmonary disease (COPD), heart disease, obesity, diabetes and renal disease. The database contains some information to inform ethnic and gender differences in parameters; however, the majority of the published data pertain to Asian and Caucasian males. In addition to a general lack of data for parameters in older people with different health conditions, there is also a lack of information on blood and tissue composition in all older groups. Despite these limitations, the database represents a potentially useful resource for the parameterization of PBPK models for older people to facilitate the prediction of dose metrics in older populations for application in risk assessment.	
6	The move towards providing guidance on the requirements for Physiologically Based Pharmacokinetic (PBPK) modelling is to be applauded. The recognition that PBPK models can change over time as more data becomes available to inform their parameterisation is also welcome. In the qualification process it is welcome that it will be possible to use peer	General agreement. Of note qualification by e.g. learned societies has been replaced with e.g. 'peer reviewed literature'. The use of data for qualification from other data sets is also included.

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	reviewed references to support the qualification of PBPK platforms and providing a list of references is possible. We believe the platform qualification is currently narrowly defined in the guidelines and should be broadened. For example if a PBPK platform can accurately predict competitive inhibition for one or two enzymes for say a set of 15 drug-drug interactions, then the platform itself should be considered as qualified for the prediction of competitive inhibition as the underlying mechanism is the same in all cases, irrespective of whether it is CYP2D6 or any other enzyme. What needs to be assessed is whether Ki values can be accurately assessed in vitro for all enzymes but this should not be addressed as part of platform qualification. This is a separate issue. Overall a lot of good points are made in the draft guidance but in many places the guidance appears to be written from a population-PK/statistical fitting perspective and this is not always appropriate for a PBPK modelling exercise. For instance by their nature a PBPK model will not be uniquely identifiable in most cases. Whilst sensitivity analysis can show the importance of certain parameters to the overall simulation performing a formal identifiability analysis would not be overly helpful. Likewise conducting a sensitivity analysis for every parameter (global sensitivity) that can influence the outcome of the simulation (L417) is unlikely to be informative. Changing tissue blood flows and organ sizes for instance will change the pharmacokinetic profile but it is not clear how performing a sensitivity analysis to show this is relevant without some scientific justification. We believe the use of sensitivity analysis should be targeted/specific to parameters which are key to the application of the model (e.g. Ki values for assessment of DDI liability for perpetrator; fmCYP3A4 for victim drug), or have uncertainty and/or where specific	Global sensitivity analysis is no longer recommended instead the focus in on key parameters for the intended use. Accuracy of prediction is considered hard to pre-specify instead it is suggested it should be considered in terms of the known concentration effect relationship for efficacy and safety.

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	assumptions have been made and these have significant impact on the simulation outcome. In terms of qualifying a PBPK platform it is difficult to assess the impact as that will depend not only on the platform but also on the information provided specifically about the compound of interest. With the same platform and underlying data it would be possible to have scenarios that would adequately meet the requirements of a high impact scenario (eg a compound where the fm by CYP 3A4 is adequately described by the in vitro data and verified with a strong CYP 3A4 inhibitor in vivo, with the submission aiming to make recommendations for how the compound will behave when co-administered with a moderate CYP 3A4 inhibitor) and also with the same platform the same scenario with another compound where this would not be appropriate (e.g. where the in vitro data is inadequate to describe the fm by CYP 3A4 accurately and there is no other verification of the values used). In both cases the platform with underlying equations and algorithms are the same. Using a bottom up or middle out approach to develop PBPK inhibitor files in general will allow the pharmacokinetics of an inhibitor compound to be simulated. Showing that the compound file can recover the AUC change of probe substrates in in vivo DDI studies is important but the intention of the PBPK model building is not in general to fit the model to observed in vivo profiles so if the in vivo AUC ratio is adequately recovered what limits would be proposed for a model to recover individual PK parameters (eg Cmax, Tmax, AUC, half-life etc). It is recommended that sensitivity analysis is going to be used to “detect” the in vivo perpetrator potential, what limits should be set? If sensitivity analysis is performed to investigate the impact of driving the Ki down (e.g. 10-fold) and increasing the hepatic uptake (e.g. 10-fold), this is potentially increasing the DDI liability by 100-fold. A recommendation should be put in place to accommodate such scenarios	

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	otherwise a clinical study will be required for every DDI liability flagged by the in vitro inhibition data. In several places eg line 267 it is mentioned that accurate predictions of inhibition should be demonstrated but nowhere in the document is the necessary accuracy defined. This could be dependent on the impact of the PBPK model and the level of clinical data available to verify the model. However, it is not always possible to have the perfect dataset whereby extensive clinical DDI studies have been conducted and can help verify the relative contributions of the different clearance pathways. For oncology drugs, this is an issue and needs to be reflected in the level of accuracy required. For enzymes such as UGT 2B7 that are expressed in the kidney and liver it is not possible without invasive measurement to know whether the action of an inhibitor at each site of the enzyme is adequately predicted. Yet it would be possible to show that the overall effect of the AUC change in plasma could be predicted. In this scenario could a model be qualified for certain uses. Indeed, for many drugs that are being developed, where solubility is an issue, it is not possible to perform clinical studies involving IV and oral. So it is likely to be an issue to elucidate the contribution of an inhibitor in gut and liver and especially kidney. One of the three approaches to qualify the PBPK platform is through "learned Societies". While this is a great additional opportunity for qualifying models this approach is not adequately explained both on the definition of such societies and the qualification procedure.	
8	We recommend more clearly stating the two types of regulatory decisions the PBPK modelling can be used for.	Comment unclear.
9	This document covers some general views and comments on the 'Guideline	The comment contains a series of specific comments which

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	on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (draft)' (EMA/CHMP/458101/2016). The intentions are to constructively highlighting certain general aspects and so hopefully contribute to the comprehensiveness, coherence and durability of the guideline. First, I commend the initiative of composing a guideline for physiologically based pharmacokinetic (PBPK) modelling in a regulatory context. As noted in the draft, a PBPK models facilitate the possibility to combine physiological, physicochemical and biochemical aspects for integrated simulations, predictions and translations. PBPK modelling has a great potential to be used in drug development and EMA should provide for that this tool can be used to the benefits of patients, without compromising safety. The draft guideline offers information of how EMA intend to structure PBPK model (platform) qualification and evaluation of specific drug models. However, on a certain number of aspects the guideline is somewhat ambiguous and would benefit of further clarifications. The PBPK guideline should, in my opinion, promote general application of PBPK modelling. However, on certain aspects more details and specifications may be needed, in analogy with other guidelines e.g., guideline on Bioequivalence: blood level bioequivalence study and the guideline on Good clinical practices. The purpose and implementation of the guideline should naturally be in strict line with the EMA mission of scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU.	have been addressed in the text in the relevant sections. Of note clearer distinction has been made between qualification of the PBPK platform and evaluation of the predictive performance of the drug model by presenting these as separate appendices. EMA does not routinely re-run models at this stage, which is why the requirements for model evaluation may be considered high. It is also not possible to make data sets publicly available, but EMA tries to exemplify acceptable qualification data sets by way of external presentations and publications.

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	PBPK model - definition: There is very little guidance to the requirements for a model to be classified as a physiologically based pharmacokinetic model, i.e., "What are the requirements in order to fall under the PBPK guideline?" Following information is presently given in 1. Introduction: *"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."* This information provides a good outline of the general PBPK concept but doesn't include any details of the boundaries to the model/model structure. Will there be any guidance to recommended model structure, approaches of physiological links, level of details etcetera? If this is not provided within the guideline it would be very beneficial to make model qualification decisions and motivations publically available (both qualified and disqualified) so that future PBPK model development can be based on this (indirect information of necessary requirements for qualifications). For example, the compartmental approach is currently the most commonly adopted method to model tissue drug concentrations in PBPK models applied in drug development. However, there are other, albeit more complex, alternatives to this approach, e.g., fractal approaches to describe heterogeneous tissue drug distribution. If less traditional strategies also are acceptable under the PBPK guideline the EMA needs to prepare for such model evaluations. Related to this aspect, is the evaluation of the level of a PBPK models scientific accuracy and physiological resemblance/description. On one side are the simplifications of nature (physiological, biological, physical and chemical) that are inevitable in contemporary modelling. On the other side	

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	is the limitation to measure processes/exposure and the related issue to include mechanics in models that isn't (cannot be) verified. There is also the aspect of what level of details that are needed for the specific purpose. These aspects are many times related to scientific disagreement and EMA will have to consider carefully where to put the boundaries for model simplifications and inclusion of unverified processes as this will be precedential for other models. Without any guidance of requirements and/or outlines the model developers will need to either consult EMA or wager that the model will be in accordance to EMAs views. This will most likely lead to unnecessary delays and efforts for developers and EMA, which will be resource consuming for both parts. This will also increase risks for subjective case-by-case EMA decisions of adequate model structure/parameters/level of details. Lastly, will there be a cost for EMA model advice and guidance? **Application of PBPK models:** The paragraph "3. Scope" describes current EMA experiences and regulatory submissions that have included PBPK modelling. Primarily this is within DDIs and paediatric investigations and throughout the guideline there are examples and links to these applications. However, the paragraph states that "*The guidance may, however, conceptually be applied when qualifying a PBPK platform for use in any area*.". This statement is of highest significance and I fully support it. Therefore, to emphasize the general application of PBPK models, and reduce the focus of the guideline to DDI and paediatric investigations, I would suggest that examples of application, e.g., paragraph 4.2.1 (Example 1 & 2) and paragraph 4.2.3, is relocated to an appendix or supplementary information repository of	

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	specific applications of the guideline. **PBPK platform vs Drug model - Qualification:** Although specified in "Definitions", the distinction and relation between PBPK model (platform) and drug model is not always obvious in the present draft. The interpretation of the draft is that the development of a drug model can include changes to PBPK model structure and system parameters (5.5.3 Drug model structure), introducing the possibility to alter fundamental PBPK model aspects in a PBPK platform. Construction and verifications are also mentioned in the context of description of drug model building (5.5.1). However, changes to such fundamental PBPK model aspects in a PBPK platform will make a previous general qualification towards a large model drug dataset redundant. The content in paragraph "5.5 Drug model" presently signifies that EMA will consider tailor-made drug specific PBPK models and that a general qualification of the PBPK model is not always needed. However, this is not in alignment with the information given in the "Executive summary" and paragraph "4. Qualification of the PBPK platform". From the other perspective, it seems highly irrational to qualify a PBPK model (platform) towards a qualification data set, and then in the specific drug investigation make changes to fundamental model components so that the model performs adequately for the particular drug. By doing such alterations the PBPK model qualification is no longer valid. To adjust drug specific parameters may be appropriate in certain cases, but adjustments of model structure and system parameters is in contradiction to the purpose of the qualification. The distinction of "Drug model" and "PBPK platform" needs to be clearer, especially regarding the essential PBPK model. There are currently overlaps and ambiguousness in the definitions as well as in the text that make interpretations and application of the guideline difficult,	

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	especially concerning the qualification procedure. **From "Definitions":** ***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.* ***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.* **Transparency:** There is no general information regarding transparency of the qualification processes. However, at the EMA workshop on this topic in December 2016 the impression was that transparency would be highly restricted, both in terms of model details, model qualification and qualification datasets. Still, the guideline refers to that a specific PBPK platform (and I assume also model) can be qualified via the CHMP qualification procedure (EMA/CHMP/SAWP/72894/2008). In that guideline under paragraph "operations" there is a strong indication of full transparency: "In addition a public consultation will be pursued prior to a final qualification opinion to take the views of the scientific community into consideration. The public consultation of the scientific community will ensure that CHMP/SAWP shares information and is open to enlarged scientific scrutiny and discussion. The timing of the public consultation will be agreed with the applicant, who will also have the opportunity to remove any confidential information from the document to be published. The operational sustainability of the process will require the levy of appropriate	

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	assessment." Is this process also going to be applicable for PBPK models/platforms? There is an innate contradiction to this as very little (if any) information can be removed from a PBPK model without affecting its functionality. Related to the model qualification process it is vital that EMA has a well-defined strategy for how to deal with information and data that is planned to be kept confidential (e.g., assessments, input data, system data, model structure/equations, model assumptions, EMA comments and considerations). If details of the qualification are undisclosed there is a high risk that the integrity of decisions/qualifications made by EMA will be questioned. This will have an overall negative impact on the EMAs credibility as an unbiased institution in this field. My strong recommendation is that - Maximum level of details (preferable all) related to the PBPK model should be made publically available. The most straightforward approach for this is to disclose the full PBPK model code and all assumptions and system parameters. - All qualification datasets are made publically available (both for qualified and disqualified models). - EMA comments and considerations are made publically available **Model or platform:** The draft guideline ambiguously focus and links the words "model" and "modelling" to software platform, i.e., an application software, that is related to installation, version control, compound files, verification etcetera. However, the central aspects in the guideline should relate to the functional	

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	mathematical model itself, i.e., model structure and equations, approaches for description of physiological processes, how system parameters and compound data are interacting, integrated and translated, etcetera, and finally how this is composed into the operational mathematical model (i.e., scripts and code). It is not completely clear if the guideline for qualification also will apply for models in the format of script/code or if an interface is needed, to create named PBPK platform/computer program. With code/script format means that the PBPK model is described as the operating code, equations and parameters, in a programming language. To use/run the PBPK model (script/code) a specified executable program is then needed, however this program itself is not the PBPK model. The similar term "Computational model/solver " is defined in "Definitions" but only in relation to a "computing platform", both these two definitions are not addressed further in the guideline. The code format of a PBPK model is completely transparent and should from a regulatory perspective be optimal, as statements and model assumptions, processes, scaling factors, implementation etcetera can be verified directly. If the PBPK model code is written in a language executable by a common or open source program the model can also be used by the regulatory evaluators in practise which would extremely beneficial for the evaluations. In all, submission of a model in code format is not only easier to evaluate, scrutinize and communicate; it also enables the EMA evaluators to run the model themselves and thereby verify that the presented modelling results (qualifications and drug models) are correct. This model format should therefore be preferred and endorsed by the EMA in my opinion.	

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	Qualification data set: There is no guidance for the composition of the qualification data set or a strategy to how the qualification data set will be evaluated. Such strategy is extremely important as the model (platform) qualification is completely dependent on this data set. The guidance should also include a strategy for how to address availability of multiple measurements/variability in input parameters. Equally important is a strategy for how to handle cases when experimentally measured input parameters are missing. It is for a number of reasons, foremost for patient benefit and safety, essential that qualification data sets are made publically available. This will ensure - Public evaluation of the data - Data variability assessment (Intra-lab) - Data updates as knowledge increase - Efficient and future model development / qualifications - Integrity for EMA qualification decision Also, public availability of qualification data sets will in the long run create a very valuable data base that can be used for future PBPK model development that would aid drug development for the benefits of patients. The sustainability and accessibility of such data base is therefore warranted. For certain applications there is an option, or recommendation, to use predicted input parameters, e.g., predict lipophilicity (logD) from physicochemical descriptors rather than to use experimental measurements. How will these external prediction models be evaluated and the impact on PBPK model predictions assessed? EMA will need to construct, and preferable make public, a detailed strategy	

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	for these aspects to prevent risks for subjective qualification data sets and case-by-case decisions. **Feedback on PBPK model performance:** A strategy for feedback and reporting of qualified model performances needs to be put into place before the guideline is finalized and launched. Such feedback will be essential for continuous evaluation of the models quality and application. Valuable and important information will be produced if/when additional qualification drugs are analysed or if the model user applies a different set of input parameters (generated from the user's lab) than was applied in the original qualification. Also, information of model performance will continuously be generated by the application of the model. Such an example could be to compare prospective PBPK model predictions for guidance of dose selection with the final outcome of the clinical study performed. In a patient safety perspective it is of uppermost importance that the qualifications of models that performs arbitrarily and unstable (by a set criteria) are recalled or that risk warnings are publically announced. EMA will need processes that ensure that model prediction failures can and will be reported. Similar processes are needed for management of information of additional/new qualifications/evaluations of the PBPK model/platform. **Model accuracy and precision:** Some guidance for model accuracy and precision would be recommended to provide in the guideline, there are currently not specifications of this in the	

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	guideline draft. Defined criteria for success and failure are central for the model qualification. This also applies to the question of if/when a model qualification should be retracted. **Evaluation of the drug model (5.5.6):** *"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."* In this context it is not clear what is intended by the phrase "*Otherwise it is necessary to refine and update the model with more ADME data.*" Which model can/should be refined and updated? Is it new experimental data/information of the investigated drug or can parameters be estimated to fit the model (5.5.2)? Should additional processes be integrated in the PBPK model (platform) or can subjective adjustments be made according to 5.4 and 5.5.1? This option opens the door for many alternatives and the evaluation of this will be very difficult. For instance, how will a scenario be handled where several different adjustments can accomplish the same improvement in model results? In analogy with previous comments, the option to make drug specific PBPK model changes makes the qualification process of the PBPK model somewhat pointless, as the final model will be different to the original qualified one. **Practical aspects:** To construct a model is relatively inexpensive (depending on the complexity) and a qualification can readily be made for certain low-risk	

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	compounds and applications. There is therefore a possibility that EMA will receive a substantial number of models for qualifications. EMA needs to estimate the level of cost related to model qualification and relate this to available resources. Potentially, EMA will need to set a strict framework for evaluations and appoint a number of highly qualified model evaluators to ensure qualification integrity and to avoid biased qualification decisions. System testing (bug control, syntax and mathematical errors) is relative expensive as it doesn't generate money per se. This task is therefore by nature kept to a minimum by software companies. EMA must be ready to evaluate, and perhaps redo, system tests so to verify that these have been adequately performed. This also encompasses the task to confirm that stated mechanisms and processes are used and implemented correctly. Such activities demands highly qualified personal (technical and scientific) and are resource consuming. An associated question is therefore if there is going to be a fee for model qualifications?	
10	EFPIA welcomes the PBPK guideline and is keen to work with EMA to put appropriate practice in place. EFPIA expects that its constructive feedback indicates companies' willingness to work with EMA on developing a practice that works well for all parties. As might be expected, interest in this important guideline was quite high since 14 EFPIA companies sent comments to the draft guideline. In addition to the comments on the text as detailed below, here are some important points to highlight first: • **Qualification definition**: The guideline would benefit from a clearer separation of platform and "PBPK model for regulatory submissions" related topics. The two terms are sometimes loosely interchanged in the text. Although the definition of a platform is provided in the definition section, it would help if a short description is provided of a	The comment contains a series of specific comments which have been addressed in the text in the relevant sections.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	platform in the introduction part (Line 65 and further), together with a clarification of how a platform can be used to implement a model, i.e. how is a PBPK model different from a platform. See below a couple of points that need to be addressed in this respect (examples may help). Both platform and PBPK model need to be qualified for their purpose, but obviously the qualifications are very different, because a platform is more generic than a model, and a platform is often a piece of software. The part that defines the qualification (see e.g. L528-531) is not very clear for specific PBPK models developed for a regulatory submission. Additionally, libraries could be considered as a series of PBPK models for various compounds implemented by the vendor using their own platform. • **Accountability/responsibility for qualification:** With regards to qualification, specifically for commercial PBPK tools, a clearer separation of the drug-dependent (from the sponsor) & drug independent (software provider) components would be helpful. This would allow separating the "role" of the sponsor from the role of the software provider, even if there is an increasing awareness of the PBPK software vendors (Simcyp, GastroPlus, PKSIM) regarding qualification, they need to be more closely involved in the PBPK platform qualification (i.e. population and compound library files). • **Version control of the PBPK platform:** the need to re-perform all submitted PBPK modelling in the latest software versions is a real concern. It could become a major overhead and could thus limit the use of PBPK by sponsors or delay the simulations if there needs to re-qualify the model with the latest version. A sponsor that includes PBPK modelling in a submission should be able to use a platform that was	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	approved by the agency for a series of purposes without the need to reconsider the qualification question of the platform for each new submission. The sponsor should rather focus on the specific PBPK model(s) developed for the submission package, including interactions of the drug candidate with relevant other drugs, and different physiologies (animal, children etc.), but unique for the submission. The purpose and validity of this modelling in the context of the submission should also be addressed by the sponsor. • **More clarity on other common uses of PBPK would be useful in the final guideline:** in the draft guideline, the focus is mainly on "high impact regulatory analyses", and in particular on DDI and paediatrics, which probably reflects the experience of the Agency. It is indeed possible to apply the principles laid out in the draft guideline to other areas of PBPK applications, but details vary for applications such as supporting human dose prediction, prediction of absorption and formulation effects, and prediction of the effect of organ impairment or genetic polymorphisms on PK. It would therefore be of great benefit if the final PBPK Guideline could reflect a broader use of PBPK M&S, e.g. biowaivers, extrapolation to special populations, food effect. The agency's position on acceptability of applications of PBPK modelling and simulation for drug metabolizing enzyme induction (such as CYPs) would need clarification since there is currently no mention of this application in the guideline and this is now a widely used application of PBPK. Moreover, the use of a very limited number of examples may lead sponsors to be too cautious in the submission of applications of PBPK modelling. It is therefore suggested to list more scenarios such as applications for earlier development stages and applications such as predicting formulation, food or PPI-related DDI. Finally, it would be	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	useful if the Agency could clarify its position on requirement of clinical intravenous (IV) dosing data for PBPK model building. The importance of IV dosing in aiding the understanding of drug disposition of orally administered drugs needs to be emphasized, especially for drugs that are transporter substrates, or possess poor solubility, CYP3A-mediated metabolism and phase II metabolism. Without iv studies, understanding of mechanisms underlying exposure can be compromised and the benefits of applying of sophisticated modelling can be lost. • **Provide information on medium and low impact applications and consequences associated with the software qualification:** the draft guideline provides detailed information for high-impact analyses, but very limited guidance on moderate and low level impact analyses. As experience with PBPK applications at different impact levels is gathered, the guideline should become more specific as to when these levels apply, and what consequences are associated regarding software qualification/model validation and reporting requirements. • **Examples of labelling claims:** It would be most helpful to provide examples of labelling claims which have been impacted to greater or lesser extents by PBPK models and simulations therefrom. • **Useful references are proposed for consideration and addition to the final guideline:** • The paper on good practices in modelling and simulation has been published by the EFPIA MID3 Workgroup in spring 2016 (Marshall et al, CPT Pharmacometrics Syst Pharmacol 2016; 5: 93–122; doi:10.1002/psp4.12049). Although covering a wider scope, PBPK examples are included. This paper addresses key aspects of practice,	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	application and documentation, which are largely applicable to PBPK modelling as one application area. Insofar as they apply to the particular use of PBPK models as developed in the guidance, recommendations from this "good practices" publication should be taken into account. Link to the article: http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf • Reference to the PBPK white paper: Jones et al CPT 2015; 97: 247-262. Link to the article: http://onlinelibrary.wiley.com/doi/10.1002/cpt.37/full • It may be beneficial to leverage information from the "*Guideline On Reporting The Results Of Population Pharmacokinetic Analyses"* (EMEA 2007) for this current guidance on PBPK model building and reporting. This will ensure consistency in the requirements of the reporting structure when carrying out a model-based analysis to support a licence application or other health authority submission. • Since PBPK modelling and simulation is an example of extrapolation from prior data and information, please consider citing the EMA concept paper on "extrapolation of efficacy and safety in medicine development", the draft reflection paper on "Extrapolation of Efficacy and Safety in Paediatric Medicine Development" and the ICHE11 guideline currently under revision. PBPK M&S is essentially an extrapolation exercise. The reflection paper, although focusing mainly on efficacy and safety, does state that "the underlying principles may be extended to other areas of medicine development" and many of these principles may indeed be applicable to PBPK.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	With respect to the application of PBPK modelling, other than cross-referencing guidances on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal (CHMP/EWP/225/02) or hepatic function (CPMP/EWP/2339/02), the agency should consider formulating some guidance regarding the application of PBPK to estimate PK changes of a drug in these populations.	
11	As PBPK modelling is increasingly used within applications, the guideline to outline requirements for content of PBPK modelling and simulation reports is much appreciated. This will be very helpful for companies and assessors. Given the complexity of such PBPK platforms, qualification of the PBPK platform by a CHMP qualification procedure (EMA/CHMP/SAWP/72894/2008/Rev.3) is much encouraged. The focus of the guideline is on interactions due to CYP inhibition. However, transporters may play an important role in DDIs (especially if the rate-limiting step is transporter mediated uptake in the hepatocyte). It is acknowledged that current scientific knowledge is not enough developed to incorporate transporters into PBPK modelling, but some mentioning would be appreciated. It is noted that only for the first time in Section 5.5.4 on sensitivity analysis the requirement of an analysis plan is mentioned. Should this requirement not be mentioned earlier in the guideline on a more prominent place?	The comment contains a series of specific comments which have been addressed in the text in the relevant sections. The focus of the guideline is in line with the experience of EMA to date in terms of models that have been submitted to support regulatory decision making. Details have been included e.g. *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*. Reference to an analysis plan is now included in the section on model development.
12	The guidance is too focused on DDI applications, while all PBPK applications should be addressed to provide a more useful guidance. The guidance asks for large qualification datasets without specifying what is considered to be "large" dataset. We suggest that higher emphasis should be placed on diverse (where applicable) rather than large datasets. If sponsor company did not use the latest version of the platform, the draft guidance requires justification for this decision. The guidance should recognize that it may not be feasible for the sponsor company to always use the latest version:	The focus of the guideline is in line with the experience of EMA to date in terms of models that have been submitted to support regulatory decision making. For version control the statement is made that *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*

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	• Companies go through strict internal validation of each new software version before it is released for use by scientists: there may be several months delay between the release of a new version and when the new version is available to scientists. • There might be a change in a relevant section of the platform and the change was not requalified yet. There might be changes in the underlying model assumptions that affect the simulation result and it is not feasible to rebuild the entire model with new assumptions in the available timeframe. One of the strategies for PBPK platform qualification is CHMP qualification procedure, which would be preferred by all involved parties as it simplifies the subsequent application and review process. However, as it is a lengthy and expensive process, some clarifications of the procedure are needed to help with the decision to go down this route: • how much of the software capability can be covered in a single CHMP application? • can models for multiple DDI substrates and perpetrators be lumped into a single CHMP application? what will be involved in requalification of subsequent software versions? Once a software has been qualified for a series of simulations, updated versions should be considered qualified for those simulations as long as the results obtained from the updated version are, for all practical purposes, equal to the earlier results. This allows for very slight differences that might result from changes in the flow of mathematical and logical calculations while effectively producing results that are different by amounts too small to be statistically significant.	*updated new version(s) should be justified if the new version is to be used for a regulatory purpose.* A number of options for qualification remain open.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
52-54	8	**Comment:** We suggest that additional clarity be given to the types of regulatory decisions that could be supported through PBPK models, in relation to the pathways for submission of such models for potential qualification (MAA applications versus submissions through the Novel Methodologies in Drug Development pathway).	Not accepted. This level of detail is outside the scope of the current scientific guide.
61	3	**Comment:** rephrase: a PBPK model is defined as one that… **Proposed change:** a PBPK model is a mathematical model that simulates…	Accepted. Text amended.
64	4	**Comment:** two full stops. "physiological, physicochemical and biochemical determinants. The majority of PBPK regulatory.	Accepted. Text amended.
65	3	**Comment:** PBPK platform (happy to see that is defined in the Definition section). What is the difference between platform and software?	Accepted. Definition of a PBPK platform provided. Software is a broader term.
65	10	**Comment:** PBPK platforms are nicely explained in the definition section. Though, some clarifying words already in the introduction would be appreciated. A terminology table is proposed for consideration	Accepted. Text amended.
68	3	**Proposed change:** These include consequences …	Accepted. Text amended.
68	4	**Comment:** include rather than includes. "These includes consequences of assumptions made"	Accepted. Text amended.
71	4	**Comment:** Is it possible to give more guidance on how many external data sets are required?	Accepted. Text amended.
71	4	**Comment:** adequate rather than adequately. "The PBPK platform needs to be qualified for the intended use by showing adequately prediction of"	Accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
76	4	**Comment:** As clinical pharmacology studies are aimed to address a number of questions beyond informing models, please consider rephrasing this as "it is recommended to use the opportunity to design clinical pharmacology studies to provide data to successively….."	Accepted. Text amended.
76-78	1	**Comment:** in that sentence, it seems that the studies should be designed to support the model: a Model Based Drug Development. The studies are generally designed on the basis of the current knowledge with the aim to answer to specific questions or to fill certain gaps. Modelling and simulation can certainly help in the design; not sure it drives the design. **Proposed change:** if the sentence was modified "that the *in vitro and/or in vivo* clinical pharmacology studies" this would be OK.	Partly accepted. Text amended.
81	3	**Comment:** First in human trials **Proposed change:** First-in-human clinical trials	Accepted. Text amended.
81	7	**Comment:** The document contains no description about content required for submission to support dose selection in first-in-human trials. Could guidance be given on this topic?	Not accepted. This level of detail is outside the scope of the current scientific guide. For the purposes of the present guideline first-in-human trials would be in the 'low impact' category.
82	10	**Comment:** Update sentence with "…confidence in its utility increases" for increased clarity. **Proposed change:** "However, it is expected that the extent of use of PBPK modelling will expand as additional system knowledge is gained and confidence ***in its utility*** increases"	Accepted. Text amended.
83	3	**Comment:** sponsormay **Proposed change:** space between two words	Accepted. Text amended.
83	4	**Comment:** Space required after sponsors. "For the qualification of PBPK platforms for an intended purpose, sponsorsmay apply for a	Accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Committee"	
83-89 and 133-138	10	**Comment:** For commercial software, it is requested that it is the responsibility of the commercial software company to apply for a CHMP qualification for the PBPK platform intended purpose in general including software supplied compound files.	This is beyond the remit of the guideline. It is the responsibility of the applicant to ensure a suitable qualification is provided, this could come from the commercial software company, if one is used.
84	10	**Comment:** The formal process of CHMP qualification takes more than 6 month and Simcyp release its updated version each year. How the qualification process should be appropriately aligned?	Partly accepted. This is addressed in the guideline under version control.
86-87	8	**Comment:** The word "supported" is unclear. C-Path suggests use of the word "pursued" instead. We also suggest that Public-Private-Partnerships (PPPs) such as pre-competitive consortia, be added the examples of non-drug developers who may pursue qualification. **Proposed change:** "In the future qualification may also be supported pursued by other types of groups, e.g. learned societies, public-private-partnerships."	Accepted. Text amended. The concept of qualification by learned societies has been found to be confusing in the consultation and so the example has been changed to 'peer reviewed literature' but other options are possible.
87	1	**Comment:** what are the learned societies?	Accepted. Text amended. The concept of qualification by learned societies has been found to be confusing in the consultation and so the example has been changed to 'peer reviewed literature' but other options are possible.
87	2	**Comment:** Clarify qualification by 'learned societies'	Accepted. Text amended. The concept of qualification by learned societies has been found to be confusing in the consultation and so the example has been changed to 'peer reviewed literature' but other options are possible.
87	4	**Comment:** Please add a definition of "learned societies" to the appendix.	Accepted. Text amended. The concept of qualification by learned societies has been found to be confusing in the consultation and so the example has been changed to 'peer reviewed literature' but other options are possible.
441, 87	4	**Comment:** Please clarify if the seeking of CHMP Scientific Advice is	Not accepted. This level of detail is outside the scope of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
and 151		foreseen as a part of other Scientific Advice meetings or as special meetings for PBPK modelling?	current scientific guide and is the choice of the applicant.
87	10	**Comment:** Please clarify what is meant by learned societies. See also related comment on line 144.	Accepted. Text amended. The concept of qualification by learned societies has been found to be confusing in the consultation and so the example has been changed to 'peer reviewed literature' but other options are possible.
119	3	**Comment:** add full stop at the end of the sentence.	Accepted. Text amended.
120	10	**Comment:** Please consider using "drug-drug interaction" instead of "drug-interaction" for consistency.	Accepted. Text amended.
124-126	3	**Comment:** I do not understand the sentence. Specific examples on how to apply this guideline to other areas are not given. What other areas??? **Proposed change:** Within the medicine community I assume, can we state again which areas maybe by brackets.	Accepted. Text amended.
129	4	**Comment:** explicitly rather than explicit: "the ability of the platform to perform that specific type of simulation should always be explicit"	Accepted. Text amended.
128-132	10	**Comment:** This paragraph should be further clarified. For example how large should the dataset be relative to the model development dataset; does it need to be from separate studies **Proposed change:** "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 ***(including different versions)*** should be qualified for the intended purpose) using external data ***(i.e. data that are not used in model or platform building)***.	Accepted. Text amended.
127-316	10	**Comment:** This guideline is somewhat vague regarding the requirements for the PBPK software. Based on current trends, it is	Not accepted. This level of detail is outside the scope of the current scientific guide, but confidence intervals on

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		anticipated that DDI predictions will constitute a major portion of the PBPK modeling packages submitted in support of a regulatory file. It will be crucial to predict not only the geometric mean AUC, Cmax, AUC ratio and Cmax ratio, but also the confidence intervals associated with these parameters. This implies that the software would have to have some Monte Carlo capabilities to allow a simulation of the population variability. This may be obvious for commercial platforms such as Simcyp and PK-SIM, but not necessarily for in-house built software platforms.	parameters are recommended.
130	3	**Comment:** using external data **Proposed change:** add example of what is meant by external data. Data not used in the initial calibration of the model?	Accepted. Text amended to remove reference to 'external'.
130	4	**Comment:** Again it would be helpful to have in the guidance a clearer definition of what is meant by external data.	Accepted. Text amended to remove reference to 'external'.
131, 171, 192, and Section 5.7	10	**Comment:** Suggestion to state not only in line 171, but also in lines 131 and 192 that the safety of patients (co-) determines the impact. Or perhaps one could speak about "subjects", since they will not all be "patients", i.e. with a disease to be treated. The safety aspect could be mentioned again in Section 5.7. However, it is not entirely clear whether the focus is on the safety of study subjects (during drug development) and/or real-world subjects after market-authorization.	Not accepted. This level of detail is outside the scope of the current scientific guide.
132, 257	2	**Comment:** Guideline favours use of commercial software packages (vs. custom built). Clarify role of software companies/sponsor in model qualification with different versions	Not accepted. This level of detail is outside the scope of the current scientific guide.
133-138	8	**Comment:** "*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.*"	General agreement.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This is an extremely valuable statement that should be bolstered in the document. Linking the PBPK guidance document with the Guidance to Applicants for the Qualification of Novel Methodologies for Drug Development represents value added for the submission by pre-competitive consortia of MAA-independent PBPK platforms for potential qualification.	
133	10	**Comment:** Remove "A" from "A qualification" to just "Qualification" for an action-statement. It is suggested to include the URL to the relevant EMA web site and to also include "EMA/CHMP/SAWP/72894/2008/Rev 3" in Section 2. **Proposed change:** ~~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).	Accepted. Text amended.
134-136	4	**Comment:** Regarding the EMA web site which will list the qualification documents for the PBPK platform (and version). Please provide more detail on this and whether it will be possible to use this as a definitive resource for the most recent list of qualified components. A link in the guideline to this site will be helpful.	Not accepted. This level of detail is outside the scope of the current scientific guide.
134-138	10	**Comment:** It is not clear how the CHMP will qualify a certain version of a PBPK platform, and whether the criteria proposed in this guidance will apply when qualifying a version of a platform. If a certain version of a platform gets the support from the CHMP, does it mean all the compound files, system parameters, etc are qualified or just certain parts of the platform? These details are not in the CHMP qualification procedure and should be clarified. It would also be an expectation that CHMP will provide adequate description and reasoning behind their opinions on any qualification plan they intend to put on their website so that sponsors and software vendors will	Not accepted. This level of detail is outside the scope of the current scientific guide.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clearly understand the reason behind any decisions.	
136	7	**Comment:** "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." **Proposed change:** Could you please add a link where on the web site the qualification for intended use will be presented?	Not accepted. This level of detail is outside the scope of the current scientific guide.
137	4	**Comment:** missing word "to"	Accepted. Text amended.
139-141	10	**Comment:** This is not to be preferred, because platforms are generic, and submissions are drug specific. A generic platform is supposed to handle multiple cases. **Proposed change:** Handle platform qualification and assessment of PBPK models for regulatory submission separately. Alternatively, if the PBPK model is tailor-made and a generic platform was not used, the PBPK model could be assessed as any other model in a regulatory submission.	Partly accepted. Text amended. This is in line with what is already proposed.
142	4	**Comment:** Please clarify if all work published in peer reviewed journals are considered qualified, as long as "the included validation dataset is described in sufficient detail to allow a secondary assessment". What if the current simulation uses a later version of the platform than the publication? Does it require a full re-qualification? As the work described in publications is often quite old this will clearly be a common situation.	Not accepted. This level of detail is outside the scope of the current scientific guide. The impact of any changes to the software on the results of the previous qualification will need to be discussed.
142	10	**Comment:** If all work published in peer reviewed journals are considered qualified, as long as "the included validation dataset is described in sufficient detail to allow a secondary assessment". Could "dataset" be clarified? If the published work uses an earlier version of the platform, does it require a full re-qualification? Please clarify. We do not think that the re-qualification using new version is	Not accepted. This level of detail is outside the scope of the current scientific guide.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		necessary. Please clarify what "sufficient detail" means i.e. does this mean that " each parameter that is used in the validation must be listed or must be listed and justified"	
142-143	8	**Comment:** We suggest providing additional clarity on how published papers can be used to support qualification, especially regarding the distinction between the use of published papers to support parameters already well established (cardiac output, for example), versus the use of published papers to support the rationale for a proposed context of use statement. Information addressing the following questions would be very useful: - Does this refer exclusively to publications that focus on external validation procedures for PBPK platforms? - In which cases would a dataset allow for a secondary assessment - Does "secondary assessment" mean a completely independent verification by EMA, or does this refer to a summary-level post-hoc analysis that could constitute a given level of sensitivity analysis?	Not accepted. The proposal to accept published papers as part of a qualification has been included for a proposed context of use. Publications can also be used to support plausibility of system parameters.
142-146	10	**Comment:** Qualification reports from commercial vendors should be considered acceptable as they may be up to date compared to literature reports or individual sponsor validation efforts. What should be included in the qualification report?	The guideline includes information on what should be included in a qualification data set.
143-146	8	**Comment:** We suggest reiterating the advice presented in the introduction (Lines 87-89) to encourage seeking scientific advice. **Proposed change:** "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	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		described in sufficient detail to allow a secondary assessment." C-Path suggests adding this sentence "**Seeking CHMP scientific advice for additional guidance on the use of PBPK modelling and simulation in support of regulatory submissions is encouraged.**"	
144	10	**Comment:** Please clarify what "learned societies" mean. The process of the qualification made by learned societies needs also clarification.	Accepted. Text amended. The concept of qualification by learned societies has been found to be confusing in the consultation and so the example has been changed to 'peer reviewed literature' but other options are possible.
149	4	**Comment:** Section 6 does not exist.	Accepted. Text amended.
149	10	**Comment:** There is no 'Section 6' in this guideline, shouldn't it be Section 5.5"?	Accepted. Text amended.
150-151	4	**Comment:** This sentence could be quite off-putting for sponsors with in-house PBPK tools. Could this be expanded and explained a little more fully. Would there be different requirements for in-house vs a commercial platform? If so what differences? Would the requirements be dependent on the impact of the model?	Partly accepted. The requirements are not different.
150	8	**Comment:** We recommend clarifying by referencing section 4.2 that discusses regulatory impact.	Accepted. Text amended.
150-151	10	**Comment:** With regard to the recommendation to seek scientific advice on the validity of an in-house computer programme, it would be helpful to know if this also applies to use of 3rd party commercial platforms. Also, it would be helpful to have more examples of what constitutes high, medium and low regulatory impact.	Partly accepted. Text amended.
153, 200 and 228	10	**Comment:** Further clarification would be appreciated on how pre-specification of the qualification process can be ensured. Should a company (PBPK software provider? pharmaceutical company?) submit a qualification protocol to EMA before starting the	A traceable document would be sufficient.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		qualification? Is there a process for this? Or is it sufficient to have traceable documentation that an outline of the qualification process has been archived before it has been carried out? How is this handled in the more general qualification procedure for drug development tools (EMA/CHMP/SAWP/72894/2008/Rev 3)?	
153-159	10	**Comment:** Would it be possible to give examples of established markers for hepatic (e.g. cytochrome P450) and renal clearance to aid in the qualification of the PBPK platforms? Most software programs perform validation of these known drug markers automatically for each new version of the PBPK platform.	Not accepted. This level of detail is outside the scope of the current scientific guide.
154-157	10	**Comment:** Regarding the range of pharmacokinetically relevant properties, the concept of an "*Applicability Domain*" (Jaworska J et al ATLA 2005; 33: 445-59) could be cited. In this, the "*physico-chemical, structural, or biological space, knowledge or information on which the training set of the model has been developed, and for which it is applicable to make predictions for new compounds*" is described. Ideally, thereafter, predictions should be multidimensional interpolations between compounds within a specified range of physiological conditions. Predictions for a drug or physiological scenarios outside the applicability domain may require higher levels of experimental evidence to compensate for uncertainty due to extrapolation.	Not accepted. This level of detail is outside the scope of the current scientific guide.
154-157	10	**Comment:** More clarity is needed. Is it meant that the victim drug model needs to be qualified (e.g. fraction metabolised fm) with a range of inhibitors (weak to strong)? How accurate should the extraction ratio be determined? In how many species?	Partly accepted. Text amended.
155-156	4	**Comment:** Please clarify the requirement on the different PK characteristics. Preferably specify or give examples on what is	Not accepted. This level of detail is outside the scope of the current scientific guide.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		expected for perpetrator and victim drugs. For example it is not understood why extraction ratio or permeability are important to qualify perpetrator drugs.	
161	1	**Comment:** "with adequate precision, for a wide variety of drugs", very vague statements. Clarifications would be helpful and allow more objective assessment.	Partly accepted. Text amended.
161	2	**Comment:** Define 'adequate precision'	Accepted. Text amended.
161	7	**Comment:** Please clarify why for the qualification of a platform a "wide variety of drugs" is felt to be necessary, even if a sponsor is only using the platform for one specific drug. As long as a model is well validated and predictive, why is this necessary? Also please specify what is meant by a wide variety? Several different BCS classes? Or severe and moderate inhibitors/inducers? How many constitute a "wide range"?	Accepted. Text amended.
161	10	**Comment:** Please provide how to define "adequate precision" and "a wide variety of drugs"	Accepted. Text amended.
163-166	10	**Comment:** "wide range of weak to strong CYP3A4 inhibitors..." There needs to be more detail of what constitutes " weak", "moderate" and "strong" inhibitors and how many examples are needed to qualify the platform. Also, more clarity is needed. Is it meant that the victim drug model needs to be qualified (e.g. fraction metabolised fm) with a range of inhibitors (weak to strong)? Examples are very specific to DDI and this might discourage PBPK modelling in other area (absorption etc.)	Accepted. Text amended.
164	4	**Comment:** Could guidance be given on which CYP3A4 inhibitors?	The applicant should refer to relevant guidance on drug interaction testing.
165	1	**Comment:** What is "a same set"? obtained in the same lab? using same probe substrate? same in vitro experimental conditions?	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Examples should be provided.	
165	4	**Comment:** Please clarify if "same set of background in vitro and in vivo information" is for the model substrates or inhibitor drugs in this case.	Accepted. Text amended
165	10	**Comment:** Please consider adding "same set of background in vitro and in vivo information" for the inhibitor drug to clearly differentiate form the model substrate drug.	Partly accepted. Text amended.
166	3	**Comment:** How do you represent the population? How many donors do you need to call it representative population? Is it recommended that the PBPK platform should be individual or population based ?	Partly accepted. Text amended.
168	4	**Comment:** Could the level of qualification associated with applications of high, moderate and low regulatory impact be clarified? Are some more complete definitions of the qualification requirements possible? Can the process whereby the needed level of qualification is determined be clarified?	Accepted. Text amended
168-176	10	**Comment:** Impact is not so much determined by the generic platform, but more by the context of a specific compound and how PBPK modelling is used for that specific compound (DDI, paediatrics etc). So this would have to be addressed by the sponsor as part of the submission. The task of the platform vendor would be, in the case of drug libraries and interactions, that for specific cases (the library drugs and paradigm drugs) the platform can handle these cases. Please add clarity on what process governs the determination of the level of qualification needed (high, moderate and low regulatory impact) and the size of the qualification dataset? Would prediction on other population such as hepatic/renal impairment population or Chinese/Japanese population considered as high impact?	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
178-179 and 191-192	10	**Comment:** The two statements should be consistent. See proposed rewording. **Proposed change:** All ~~simulations~~ *decisions* that affect the SmPC (Summary of Products Characteristics) are considered *to have* a high-impact ~~analysis~~. *Whether simulations in these situations are of high impact also depends on the availability of further decisive or supportive data and on the therapeutic context*. ~~This~~ High impact simulations could include […] ~~As outlined above, whether these situations should be considered high impact also depends on the availability of supportive data and on the therapeutic ontext~~.	Partly accepted. Text amended.
180	1	**Comment:** the use of PBPK modelling to avoid restriction in clinical protocol is not mentioned in the draft guideline. What kind of regulatory impact is it considered ? Is it considered at the same level as "use of PBPK in place of clinical trial"? Also, the use of PBPK for formulation development is not described in the guideline, would it be low, medium or high?	Not accepted. All simulations that affect the SmPC are considered high-impact analyses. All others as medium or low impact.
187-188	10	**Comment:** Clarification of this point is needed; see proposed rewording. **Proposed change:** ~~prediction of changes of study design of~~ *drug interaction assuming other posologies compared to* an available DDI study, ~~such as using other doses/dose regimens~~	Accepted. Text amended.
192	7	**Comment:** Please clarify what is meant by therapeutic context. Does this mean that for instance for a so-called "lifestyle" drug more qualification is necessary than for a cancer drug?	It is in terms of efficacy and safety not the indication.
195	10	**Comment:** Both examples are from the perspective of the platform vendor/developer. **Proposed change:** It would be good to have one example in the	Partly accepted. Text amended. Examples included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		context of a platform (for a vendor) and one for a sponsor developing a novel drug using a qualified platform in a hypothetical but realistic therapeutic context.	
195-239	10	**Comment:** Examples 1 and 2 relate to high regulatory impact analyses with the new drug as a victim or a perpetrator for "metabolising enzyme inhibition" effects, respectively. It would be helpful to elaborate on additional examples in this guideline, such as: "Requirements for PBPK platform validation to predict whether an investigational agent may act as a metabolising enzyme inducer in vivo"; "Requirements for PBPK platform validation for PBPK simulations of pharmacokinetics in special populations, leading to posology recommendations and relying on limited clinical exposure data." **Proposed change:** Include additional examples on "Requirements for PBPK platform validation to predict whether an investigational agent may act as a metabolising enzyme inducer in vivo"; "Requirements for PBPK platform validation for PBPK simulations of pharmacokinetics in special populations, leading to posology recommendations and relying on limited clinical exposure data."	Partly accepted. Text amended. Examples included. There are however limited examples at the current time.
202-203	10	**Comment:** Time to steady-state is not a model parameter but an output or metric used to quantitate responses.	Partly accepted. Text amended.
204	7	**Comment:** Please quantify what the agency regards as a "series of drug substances". **Proposed change:** Please add a number what EMA considers to be the minimum drug substances required.	Accepted. Detail added that eight to ten compounds is indicative of a sufficient number.
204-208	10	**Comment:** Qualification dataset needs to be clarified. How many drug substances are needed for a particular enzyme, considering various fm, fup, CL and Fg might be limited given the current	Accepted. Detail added that eight to ten compounds is indicative of a sufficient number.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substrate pool.	
207	7	**Comment:** A list of drugs per CYP enzyme that the EMA considers to be adequate for this purpose would be helpful. **Proposed change:** Please add a list to the document.	Not accepted. This level of detail is outside the scope of the current scientific guide.
210-213	10	Comment: The paragraph is confusing because the term "qualification" has two different meanings (see comments on general section). The first sentence is the qualification of inhibitor model itself, whereas the second sentence is the qualification of victim model by using pharmacogenetic data. **Proposed change:** Please consider separating these two sentences.	Partly accepted. Text amended
214-220	4	**Comment:** This text in the Example 1 is not fully clear. What is the meaning of qualified scenario? What would be the limitation of use of a model for an inhibitor obtained through a qualification dataset where fm was estimated through strong inhibition vs one where mass balance was used? Is this implying that either a clinical mass balance study or clinical study with a strong inhibitor is essential for qualification of the fm in a PBPK model? We feel that the use of fm estimates from in vitro data obtained using recombinant enzyme systems can be applicable for earlier stages of drug development and lower impact situations.	Partly accepted. Text amended
214 -220	10	**Comment:** Suggest considering the use of fm estimates from in vitro data for earlier stages of drug development and when the clinical mass balance data suggest low contribution from metabolism, even when a clinical study with strong inhibitor is not available	Not accepted. This level of detail is outside the scope of the current scientific guide.
220	10	**Comment:** It is not clear what "this specific input data scenario" is. Does this mean we can qualify in vivo fm values based on mass-balance studies and in vitro metabolism studies, so that degree of	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		DDI can be predicted? Please provide example scenarios of where mass-balance data with in vitro data on metabolite formation can be used for model qualifications.	
226-227	10	**Comment:** If possible it may be helpful to include a standard list of inhibitors and sensitive probe substrates, recommended for PBPK platform validation purposes, for the different metabolising enzymes.	Not accepted. This level of detail is outside the scope of the current scientific guide.
226-231	10	**Comment:** There is a need to differentiate between platform and PBPK model for regulatory submissions. If this concerns the platform: this would refer to DDI of library drugs with paradigm drugs (vendor responsibility). If this would concern a novel drug together with a set of possible perpetrators or victims, this would mean a limited number of "calibration" perpetrators or victims, possibly from a library, but always in combination with the investigational drug.	Partly accepted. Text amended.
228	4	**Comment:** Please clarify what constitutes a "large number".	Accepted. Text amended
228	4	**Comment:** Please clarify what constitutes a "large number".	Accepted. Text amended
228-229	10	**Comment:** "… and should include a large number of inhibitors of different potency". What would constitute a "large number" in this case? Could this be expressed in numbers to make clearer? Similarly, "If the number of known in vivo inhibitors … is limited, …". What would constitute a "limited number" in this case? Could this be expressed in numbers to make clearer?	Partly accepted. Text amended.
232	4	**Comment:** This seems to mean that a PSA is run for all test inhibitors in the qualification dataset. How should this analysis be then used for the novel inhibitor? Does the maximum range found within the test set need to be considered for the novel inhibitor?	Partly accepted. Text amended
236	10	**Comment:** The "Applicability Domain" (see above, comment on Line 154) could be cited in the statement for qualification validity	Not accepted. This level of detail is outside the scope of the current scientific guide.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
238	7	**Comment:** Please clarify whether it is admissible to use the same qualified perpetrator and substrate model to predict an interaction in a different (but also qualified) population?	This should be acceptable providing the population is qualified.
240-243	8	**Comment:** We recommend providing additional tangible examples of "moderate and low level regulatory impact analyses" beyond pediatric populations. For instance, examples on how PBPK models can be used to optimize first-in-human studies for both monotherapy and combination therapy could be provided.	This level of detail is outside the scope of the current scientific guide which focuses on high regulatory impact examples.
240-243	10	**Comment:** Are there additional examples for moderate/low regulatory impact analyses (Section 4.2.2)? **Proposed change:** … design, e.g. selection of PK sampling time points.	Not accepted. This level of detail is outside the scope of the current scientific guide.
241-243	10	**Comment:** The description of what constitutes a moderate or low level impact is very short. These categories are not clearly defined (other than by mentioning a single example for each). Examples of low impact PBPK simulation could also include PK sampling schedules. Could this section also suggest metrics for how PBPK simulations should report their findings? It could be clarified through examples as to whether full time course simulations are required, or predictions only for selected metrics such as AUC (0-t), AUC (ss,tau) and/or Cmax?	Not accepted. This level of detail is outside the scope of the current scientific guide.
243	7	**Comment:** Please clarify whether an analysis to support a dose range for a 'first-in-human' trial is classified as 'low level regulatory impact analysis'.	Clinical trial applications are assessed at the level of the national agencies. For the purposes of the present guideline first-in-human trials would be in the 'low impact' category.
247-248	10	**Comment:** This concerns a high impact application. **Proposed change:** The high impact applications in paediatrics should be moved to section 4.2.1.	Partly accepted. Text amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
254	10	**Comment:** Suggest adding the Guest et al. (2011) criteria for DDI predictions as acceptance criteria for PBPK model qualification, to avoid stringent bioequivalence criteria across large range of DDI magnitudes. Link to the article: http://dmd.aspetjournals.org/content/dmd/39/2/170.full.pdf	Not accepted. This level of detail is outside the scope of the current scientific guide.
256	7	**Comment:** A list of drugs per CYP enzyme that the EMA considers to be adequate for this purpose would be helpful. **Proposed change:** Please add a list to the document.	Not accepted. This level of detail is outside the scope of the current scientific guide.
258-278	4	**Comment:** Please clarify the process for submission of files.	Partly accepted. Text amended
258-278	10	**Comment:** Please clarify the process of submitting compound files, simulation files, and workspace files? Is the workspace file preferred in certain cases please clarify? Also, compound file may not be the right term, as a file is a format to collect and store information. **Proposed change:** rather use a phrase like "Compound properties and supportive in vivo PK data"	Not accepted. This level of detail is outside the scope of the current scientific guide.
265-266	4	**Comment:** Does this mean that an inhibitor compound model supplied cannot be considered qualified without any in vivo DDI?	Not accepted. There is a need for observed in vivo DDI data.
267-268	1	**Comment:** "If the enzyme is expressed at multiple sites, such as CYP3A4, accurate prediction of inhibition at each site should be demonstrated." Clarifications would be helpful.	Partly accepted. Text amended.
267-269	4	**Comment:** This section is not sufficiently clear. It can be very challenging to discern the effects at the different sites as relevant data are not always collected, even for many model substrate drugs. Please provide further guidance on this.	Partly accepted. Text amended.
267-269	7	**Comment:** The requirement to collect data for inhibition at each site surpasses the requirements of the EMA's "Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		medicinal products" (1 August 2012). What is the reasoning behind this requirement?	
267-269	10	**Comment:** The in vivo data to differentiate inhibition at each site are often unavailable. What are EMAs expectations regarding the experimental approaches, e.g. to differentiate CYP3A4 activities and inhibitions in gut and in liver? Can EMA clarify this requirement? **Proposed change:** If the enzyme is expressed at multiple sites, such as CYP3A4, accurate prediction of inhibition at each site should be demonstrated *using PK parameters (e.g. Cmax, AUC)*.	Partly accepted. Text amended.
269	4	**Comment:** What is meant by "suitable parameters"?	Partly accepted. Text amended.
270-274	4	**Comment:** For the estimation of the fm of the substrate please clarify whether there are any circumstances when non-clinical data could be used for fm estimation? For example for an early stage of development? For a low impact example? For a very safe molecule? Many users are relying on in vitro data for some of these cases.	Not accepted. This level of detail is outside the scope of the current scientific guideline, but emphasis is on high impact applications
271	10	**Comment:** Please clarify whether the fraction metabolised (fm) of the substrate should be confirmed using human data?	Partly accepted. Text amended: *in vivo data supporting the clearance fraction of the pathway/contribution of the enzyme (f_m) should be presented.*
272	2	**Comment:** Use of potent inhibitor to obtain fm. **Proposed change:** add 'SELECTIVE' in addition to potent.	Accepted. Text amended.
272	2	**Comment:** Use of potent inhibitor to obtain fm. **Proposed change:** It would be useful to acknowledge that although similar principle can be applied for estimation of ft (fraction transported), lack of selective inhibitors and understanding of the rate limiting processes in the disposition of the victim drug is challenging.	Not accepted. This level of detail is outside the scope of the current scientific guide.
273	4	**Comment:** Regarding the phrase "Data should support detection of inhibition at each site of the enzyme." Please clarify this requirement	Accepted. Text amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- does it refer to different sites of enzyme expression in the body i.e. liver and gut or to different binding sites of the enzyme?	
273	4	**Comment:** Assuming this refers to different tissue sites of enzyme expression then what exactly is required? For example, if this were for a CYP3A substrate would it be considered adequate to separate the intestinal and hepatic contributions via differential effects on Cmax vs T1/2?	Accepted. Text amended.
275	10	**Comment:** "When model file of commercial software is modified, it should be justified and demonstrate validity" does this mean that commercial values are always considered correct?	Partly accepted. Text amended.
279-292	10	**Comment:** "Version" is specific to commercial software and how does it fit to programs (in-house models etc.) which do not have regular update? We have concerns on the version control described in the current guidance. If the update dose not relate to the compound, the use of same old version should be acceptable in the submission. In general, we feel that the previously published work for an intended PBPK application using an old version of software should be sufficient to serve as a justification of system dependent parameters. If a model is deemed qualified for a particular version then the model should remain qualified for its intended purpose. If the guidance intends to exclude old and obsolete platforms from submission, EMA should communicate about "non-qualified versions" rather than restricting applicants to use the latest versions in the guidance.	Partly accepted. Text amended. For version control the statement is made that *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.*
282	10	**Comment:** Please provide details (how /criteria) on "demonstrate a previously performed qualification is valid for the new version"	Partly accepted. Text amended.
283	4	**Comment:** In view of the potentially enormous effort to re-perform all submission modelling in the latest software versions, please	Not accepted. It may be still valid, but this needs to be demonstrated on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reconsider the requirements for when a submission does not use the very latest software version. If a previously performed qualification is valid then why would it be necessary to demonstrate that it is also valid for the new version?	
285	3	**Comment:** What happens if these PBPK platform will not have any more financial support? If updates platform with refined/revised equations would lead to a different output? **Proposed change:** There is a need of a standardized reporting template that will report version and date of use of the selected platform.	Not accepted. Too specific detail.
Reporting of PBPK modelling and simulation	3	**Comment:** to add **Proposed change:** This section could be elaborated into a template, as an example, please see Ciffreoy et al., (2016) Development of a standard documentation protocol for communicating exposure models. Sci Total Environ. 2016 Oct 15;568:557-65. The JRC has also developed an excel template – available on request. In this section an uncertainty analysis chapter added after the sensitivity analysis is key and a table to report the uncertainty should be added.	Proposal to develop template in future updates.
285	10	**Comment:** It is suggested that if a commercial software is used by the company that supplies qualification of the platform including library compound files and populations in one version versus the next, there is no necessity to include this information in the report.	Partly accepted. Text amended.
285-286	6	**Comment:** "*Differences between PBPK platform versions should be clearly communicated and thoroughly discussed*." Some definition of clearly communicated and thoroughly discussed should be given. Communicated and discussed with whom? By what mechanism?	Partly accepted. Text amended.
285-289	6	**Comment:** "*If a given version of a platform has previously been*	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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." We believe additional clarity should be provided on the nature of support required.	
285-289	8	**Comment:** We suggest additional clarity be provided on the nature of the support required to establish the validity of such extrapolation.	Partly accepted. Text amended.
286-288	10	**Comment:** It would be helpful to have more detail on what and how much evidence is needed to extrapolate predictive performance between previous and current versions of a PBPK platform. Also, there needs to be more clarity how many versions a sponsor should keep.	Partly accepted. Text amended.
290-292	6	**Comment: "***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*." This should only be needed if the models/parameters have changed in the most recent version and are likely to have affected the intended applications.	Not accepted. This needs to be discussed on a case-by-case basis.
290-292	10	**Comment:** Documents submitted to health authorities will, very often, not contain simulations performed with the latest software version as the work is usually performed many months before submission. **Proposed change:** ~~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~~. "*Regulators may request simulations in a more recent version if significant simulation*	Not accepted. It is up to the applicant to discuss the version used up-front.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		improvements are expected due to the updated features of the software".	
293-302	10	**Comment:** It should be clarified whether the verification is intended only for in-house built platforms. Commercial platforms, such as Simcyp, have numerous published examples showing that the platform works as intended. Also, since a vendor responsibility please consider clustering all platform-related sections, and clarify what is the role of vendor and sponsor.	Not accepted. This level of detail is outside the scope of the current scientific guide.
294-301	10	**Comment:** Please remove the mathematical code of commercial models since it may not be available to sponsors as they are usually considered as an intellectual property to the owner.	Partly accepted. Text amended.
294-302	10	**Comment:** For commercial software, details of the differential equations used and parameterizations should be provided by the software vendor and therefore not requested of the sponsor.	Partly accepted. Text amended.
295-296	8	**Comment:** We recommend that a potential differentiation be made between custom modelling software and commercial PBPK platforms, and required information for each as recommended.	Not accepted. This level of detail is outside the scope of the current scientific guide.
298-299	10	**Comment:** Regarding numerical errors, it is not likely, perhaps impossible to have "no" numerical errors in a computational model. Numerical error is a specific term referring to the combined effects of truncation and round off errors. Truncation errors result from mathematical approximations (e.g. numerical differential equation solvers). Round off errors result from the finite limits of precision in a computation. Perhaps with regard to the differential equation numerical errors referred to in the cited WHO document, this should state that the differential equation integration algorithm(s) should function accurately against specified criteria for all the models to be reported.	Partly accepted. Text amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
305-311	10	**Comment:** For commercial software, the system-dependent parameters, including physiological parameters for the populations should be the responsibility of the software vendor and not the sponsor. This can be referenced (e.g. from the literature) in a simulation report, but should not be a requirement to include all the data in an appendix. If what is mentioned in Lines 83-89 and Lines 133-138, can be done by the software vendor, then this issue is addressed.	Not accepted. This level of detail is outside the scope of the current scientific guide.
305-306	10	**Comment:** It would be helpful to clarify what is meant by 'typical physiological parameters' for a certain population?	Partly accepted. Text amended
312-316	10	**Comment:** "...when installed in the computing environment..." With respect to the control of the installation process, there needs to be clarification if "computing environment" includes individual computer-loaded software or to a client-based server environment only.	Partly accepted. Text amended
312-316	10	**Comment:** The need and shape of the installation control appears unclear. Can it not be assumed that the installation of a PBPK platform is covered by more general IT system standard operating procedures (SOP) of the company / user?	Partly accepted. Text amended
313	4	**Comment:** Does installation refer to both standalone and server based software?	Accepted. Text amended
313-316	4	**Comment:** Please provide more details or examples on what specifically is needed for an installation control.	Partly accepted. Text amended
313-316	10	**Comment:** A control of the installation of the PBPK platform is asked to be performed. Please provide details or example on what specifically agency would like to see in an installation control.	Partly accepted. Text amended
314-315	1	**Comment:** "The key functionality of the program should be tested." Clarifications would be helpful.	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
314	4	**Comment:** What is meant by "key functionality"?	Partly accepted. Text deleted.
Figure 3	4	**Comment:** Please clarify if Figure 3 is specific to a victim or a perpetrator.	Not accepted. Can apply to both.
315-316	10	**Comment:** A low risk is expected for the proper installation of out-of-the-box software at the user's site, and errors are easily detected. An "Installation qualification report" is suggested to document installation according to software provider specifications, while a CHMP qualification might certify a software provider that the specifications are appropriate. **Proposed change:** The key functionality of the program should be tested. The installation qualification report should include a presentation of how this was done. ~~The installation processes should be included in a CHMP qualification procedure~~.	Partly accepted. Text amended
317-318	10	**Comment:** Section 5 describes extensive reporting requirements for high-impact submissions. Clarification should be added regarding reporting requirements for low- and medium-impact submissions.	Partly accepted. Text amended
320	1	**Comment:** Although it is clear that not all the data need to be repeated in the PBPK report, it is not clear how much of the in vivo studies that were used for the building/ evaluation/ refinement of the model need to be included. Clarification would be useful.	Partly accepted. Text amended
320	10	**Comment:** The paragraph abruptly jumps to PBPK in the context of a dossier. Propose to insert introductory wording below at the beginning of line 320. **Proposed change:** *PBPK reports should contain supporting information commensurate with the intended purpose and regulatory impact.*	Partly accepted. Text amended
324, 325	8	**Comment:** We recommend clarifying that proposed changes to the SmPC derived from the application of a given PBPK model pertains to	Not accepted. This level of detail is outside the scope of the current scientific guide.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a MAA submissions pathway, but is not part of submissions through the Novel Methodologies in Drug Development pathway.	
329	4	**Comment:** States Figure 2 is needed "if possible". Please clarify the limitations of PBPK if this is not possible and whether it is considered essential to have a study with intravenous administration to generate this diagram. Note that many companies are not generating IV data but nonetheless feel that, in certain cases, such a diagram could be generated with confidence based on non-clinical and oral data alone. A little more explanation of this figure could be useful (perhaps taken from Shepard et al.). Specific queries to the diagram could be i) it does not seem to accommodate excretion of parent in feces after an IV dose although this is often seen in practice ii) such a diagram also seems limited for description of the effect of formulation and/or food on excretion pattern.	Not accepted. 'if possible' allows for different scenarios. The diagram is only an illustrative example.
329-331	4	**Comment:** Is a quantitative mass balance diagram also needed for the drugs embedded in a commercial software that are part of the assessment or only for the investigational drug	Predictive capability of all drug models should be demonstrated but a mass diagram may not be necessary.
329-331	10	**Comment:** A Quantitative Mass Balance diagram is asked to be included in PBPK report. Is this also needed for the drugs embedded in the commercial software that are part of the assessment or only for the investigational drug, need clarification? **Proposed change:** Please provide example in situation where certain aspect of ADME are not completely known.	Not accepted. This level of detail is outside the scope of the current scientific guide.
341-347	10	**Comment:** We are in agreement that at the time of NMA submission, the outcome of PBPK model building exercises should be put in context of the concentration-effect relationship and discussed in the light of dosing recommendations. However, we strongly disagree that this should be a requirement of the 'PBPK report' since	Partly accepted. Text amended but a discussion of the results is required in terms of the acceptable accuracy of the prediction.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		it would be more appropriately placed in other submission documents where data from multiple sources (PBPK report, PK/PD report, study reports etc.) can be integrated and discussed in a cohesive fashion. The EMA guidance should only require details of the PBPK models and model building process to be included in the PBPK report. Other requirements for putting the model outcomes in context should be requirements for the package, but not the report. A related point is that PBPK models may be submitted to regulatory authorities at various times throughout the development process (e.g. clinical trial application stage, study protocols etc.). Therefore, the guidance should differentiate between guidance that is specifically referring to NMA submissions (i.e. putting exposure changes in context of concentration-effect relationship in order to justify dosing recommendations) from recommendations that would apply to submissions at any stage. **Proposed change:** Concentration – effect data should not be required to be integrated into the PBPK report. Modify to read as follows: "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."	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
341-347, 461-464, 500-502	10	**Comment:** Consequences of predicted changes in the exposure of the investigational drug with respect to efficacy and safety should not be an absolute requirement for discussion in PBPK simulation reports. The time when the PBPK modelling is carried out may be different from that of the final results of exposure-response (safety and efficacy) relationship analyses determined from clinical trials. It is therefore suggested that when there are disconnects in the timing of reports of PBPK simulations versus the availability of exposure-response information that the clinical consequences are discussed in summary documents such as CTD 2.7.2.	Accepted. Text amended
348	4	**Comment:** Please clarify the potential of pediatric PBPK for drugs which are not developed in adults as in such cases "simulations of pharmacokinetics in adults" cannot be used as support.	Partly accepted. Text amended.
351	4	**Comment:** Please clarify what is meant in this context by the phrase "the consequence of variability and uncertainty". It could be helpful to separate out these 2 aspects and explain how each should be dealt with.	Partly accepted. Text amended
355	10	**Comment:** Suggest the level and format of information to include on assumption in paediatric investigation plan e.g. testable/evaluation as outlined in MID3 paper?	Not accepted. This level of detail is outside the scope of the current scientific guide.
364	4	**Comment:** Section 5.4 discusses system dependent parameters, so what are the simulated datasets here? Please clarify the relationship to system dependent parameters.	Accepted. Text amended
367	4	**Comment:** Regarding requalification, is a literature reference, e.g. for a different Kdeg value, considered sufficient?	Not accepted. This level of detail is outside the scope of the current scientific guide.
368	10	**Comment:** The ontogeny of enzymes for paediatric modelling could be justified by using a conservative approach supported by literature references.	Partly accepted. Text amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please specify or provide examples for 'conservative approach'.	
375-376	7	**Comment:** Would it be possible to unify used wording with the FDA? Please clarify what exactly you mean by verification, evaluation, modification and refinement.	Not accepted. This level of detail is outside the scope of the current scientific guide.
375-376	10	**Comment:** process that includes construction, verification, evaluation and modification of the model. Not in accordance with figure 3 **Proposed change:** The building of a PBPK model is a continuous process that includes construction, verification, *modification*, evaluation and ~~modification~~ *qualification* of the model prior to its application.	Accepted. Text amended.
385 Figure 3	4	**Comment:** This figure seems to imply that mass-balance and iv data are mandatory for an initial PBPK model. If this is the case then use of PBPK will be strongly restricted. In many cases we believe it is not necessary to mandate these data in order to build a useful PBPK model. Please clarify the EMA position on this with reference to different levels of impact.	Accepted. Figure amended.
Figure 3	4	**Comment:** Figure 3 implies that an in vivo study with a strong inhibitor is mandatory for confirmation of fmCYP. Please clarify the need for in vivo DDI data, particularly with reference to enzymes where in vitro data indicate fm is <25%.	Accepted. Figure amended.
385	10	**Comment:** The box labelled "Drug in vivo ADME and PK-data including mass-balance and intravenous data", is unclear as to whether this is human or pre-clinical experimental animal data. Typically, initial models prior to first-in-human are built using in vitro and pre-clinical animal data and refined after human data become available, then further refined after clinical drug-drug interaction	Accepted. Figure amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		results or human ADME study plus *in vitro* phenotyping results are available. The interpretation of this box leads one to assume that mass balance and intravenous data is required for model building, which is inconsistent with the qualification of a victim investigational drug with either mass balance or clinical DDI data stated in lines 217-220.	
387-402	10	**Comment:** The guidance should specify how applicants should evaluate the uncertainty and possible correlations referred here and requirements in the report. Whether they mean uncertainty in terms of SE and correlations in terms of VarCovar of if it could be covered by a sensitivity analysis.	Partly accepted. Text amended
391	10	**Comment:** It is suggested to modify the sentence as follows. **Proposed change:** If there is more than one source of a certain parameter *with notably different values*, the value chosen should be justified and the consequences discussed"	Accepted. Text amended
395	10	**Comment:** Please clarify "otherwise justified" for logP. If it is calculated, does this require the verification of the data base that was used for the calculation?	Accepted. Text amended
396	4	**Comment:** Please clarify the EMA view on the appropriate parameter estimation procedure for PBPK.	Not accepted. This level of detail is outside the scope of the current scientific guide.
Section 5.5.3	4	**Comment:** Is this required when using a qualified commercial platform?	This level of detail is outside the scope of the current scientific guide.
399-402	1	**Comment:** There are still many unknowns leading to uncertainty and identifiability issues and unfortunately in some cases neither in vitro experiments nor clinical studies could help in decreasing uncertainty. Sometimes scientific knowledge is the limitation.	Partly accepted. Text amended.
399-402	10	**Comment:** Regarding correlation between and uncertainty in PBPK parameters more clarity on the issue is requested, perhaps through	Partly accepted. Text amended

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		the use of an example.	
399	6	**Comment:** "*Consideration should be given to whether there are parameters in the model that are correlated and if there is uncertainty in the value of more than one of the parameters. In the case that an identifiability issue is suspected additional in vitro or clinical data may be required to increase certainty in the parameters. A description on how any identifiability issues have been handled should be given*." In a mechanistic PBPK model, almost all parameters are (and have to be) correlated and in general this is not an identifiability issue. Identifiability can be an issue when one or more parameters are fitted. In those cases, the choice of estimated parameters should be justified and only in certain cases the issue of identifiability needs investigation.	Accepted. Text amended.
401-402	10	**Comment:** A clear definition of the type of identifiability in the text: parameter identifiability or structural identifiability? Proposed to change to parameter identifiability across text to allow consistency	Partly accepted. Text amended
408	4	**Comment:** Please clarify EMA view on sensitivity analyses. More guidance on the EMA view of appropriate selection of parameters and ranges for sensitivity analysis would be appreciated. In our view PSA for physiological parameters should be based on scientific rationales and existing published data. Parameters to be selected for PSA should be determine case by case as well as the range of PSA for the inputs which for in vitro parameters such as Ki, fu,p should depend on the quality of the data. Inappropriately wide ranges for PSA can lead to misleading conclusions, especially if combined in a matrix and in most cases a 2-fold range is sufficient.	Accepted. Text amended.
408	10	**Comment:** Sensitivity analysis should be included in the model evaluation part.	Accepted.

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409-432	10	**Comment:** Is the definition of "sensitivity analyses" consistent across different EMA/ICH guidance's (such as the reflection paper on extrapolation, or the emerging ICH guidance on estimands)? Section 5.5.4 seems to imply that sensitivity analyses are repeat-analyses using different parameter values. However, one may also wish to test the sensitivity to assumptions in more general terms, such as structural model assumptions. (See also lines 361 and 436.)	Partly accepted. Text amended
413	1	**Comment:** "the sensitivity analysis should be described in the analysis plan." Does it imply that a formal data analysis plan needs to be written prior to the analysis? When should the analysis plan be written?	Partly accepted. Text amended.
413	10	**Comment:** Please state simulation report instead of analysis plan. **Proposed change:** "The approach for sensitivity analysis and the range of the parameter values tested in the sensitivity analysis should be described in the ~~analysis plan~~ *simulation report*."	Partly accepted. Text amended
415	4	**Comment:** Seems to be an error in the following sentence. "The basis for the decision to go forward with as specific value of a parameter should be presented."	Accepted. Text amended.
417	1	**Comment:** the selection of the parameters for which a sensitivity analysis is (will be) performed should be justified/documented. But there is no reason to perform a sensitivity analysis "for all parameters that are likely to markedly influence the outcome of the simulated pharmacokinetics and/or the model application".	Partly accepted. Text amended.
417	2	**Comment:** sensitivity analysis should be performed on ALL parameters **Proposed change:** Plasma exposure will not be informative for some of the transporter parameters, so the sensitivity analysis may not inform model application adequately.	Partly accepted. Text amended.

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417-422	4	**Comment:** We suggest adding some words to cover absorption modeling, for example "For gut PBPK models, parameters which may impact drug absorption should be evaluated, such as gastrointestinal pH or particle size (Example Farydak drug label)."	Accepted. Text amended
417-423	10	**Comment:** The scientific rationale should be emphasized in term of selecting the parameters and ranges for sensitivity analysis. In our view, the parameters to be selected for PSA should be determined case by case; the range of PSA for the inputs (in vitro parameters) such as Ki, fu,p, should be depending on the quality of the data, and PSA for physiological parameters should be based on scientific rationales and existing published data.	Accepted. Text amended.
417-418	8	**Comment:** We recommend that additional clarification and examples be provided for scenarios where the state of knowledge of a specific system parameter (e.g., liver perfusion rates) is sufficient enough to preclude the need for additional sensitivity analyses, versus key drug model parameters for which the level of uncertainty would indeed require sensitivity analyses (e.g., transporter binding constants).	Not accepted. This level of detail is outside the scope of the current scientific guide.
421	2	**Comment:** 'parameters that are difficult to determine such as accumulation in hepatocytes..' **Proposed change:** Propose also use of mechanistic modelling of in vitro data in such cases to refine in vitro input for PBPK models	Accepted. Text amended.
427-429	4	**Comment:** Please make clearer the meaning of the sentence beginning "The consequence of the uncertainty in….". Currently it is not clear what is meant here. Perhaps a more specific example of how the uncertainty in specific parameters should be added to that in Ki would be helpful?	Accepted. Text amended
430	4	**Comment:** Please consider that the science around maturation of	Not accepted. This level of detail is outside the scope of the

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		enzymes/transporters is developing so that the definition of uncertainties in ontogeny factors may be very difficult.	current scientific guide.
Section 5.5.5.	4	**Comment:** As it stands it is not clear that this warrants a separate section distinct from the sensitivity analysis discussion.	Accepted. Text amended
441, 87 and 151	4	**Comment:** Please clarify if the seeking of CHMP Scientific Advice is foreseen as a part of other Scientific Advice meetings or as special meetings for PBPK modelling?	Not accepted. This level of detail is outside the scope of the current scientific guide.
433	3	**Comment:** This section leaves the applicant with little guidance, and would benefit from further development. Might be worth looking at the EFSA guidance document on uncertainty characterisation in risk assessment to see if there are useful concepts / recommendations that could be considered in the context of the EMA guidance: https://www.efsa.europa.eu/sites/default/files/consultation/150618.pdf	Not accepted. This level of detail is outside the scope of the current scientific guide.
443-444	10	**Comment:** Evaluation of the drug model – it would be helpful to know if this requires a 'bottom-up' approach (i.e. a model derived mainly from in vitro and physical-chemistry/physiology data) or a middle-out approach (i.e. update a bottom-up model with emerging in vivo human data to understand gap in input data).	Partly accepted. Text amended. Evaluation of the drug model would usually involve a middle-out approach.
443	10	**Comment:** How is defined "capable of predicting the observed data"? Please clarify.	Acceptable accuracy of prediction is application specific.
445	10	**Comment:** Suggest deleting "ADME" since the same may apply to any input data (not just ADME). **Proposed change:** Otherwise it is necessary to refine and update the model with more ~~*ADME*~~ data.	Accepted. Text amended
449	10	**Comment:** How the comparison with population PK analyses is expected? Please clarify	Partly accepted. Text amended
454	4	**Comment**: Are their specific measures which are preferred for	Not accepted. This level of detail is outside the scope of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		assessment of predictive accuracy e.g. %PE, absolute error, etc…? Possibly an example Table could be helpful.	current scientific guide and is application specific.
456	10	**Comment:** Regarding "pharmacokinetic data": is "data" the right term? Or "parameters", or "metrics", or "quantities"? This also links to the comment below re: lines 487 and 511-512.	Partly accepted. Text amended
459-460	10	**Comment:** While outliers in the "observed dataset" may be flagged in a model validation report, the discussion if and why they are considered outliers is usually covered extensively in the "clinical study report". Cross-reference to this source document should suffice, rather than repeating the rationale. **Proposed change:** Please delete or adapt the wording.	Accepted. Text amended
461-464	10	**Comment:** As for the comment in lines 341-347, 461-464, 500-502, it is suggested that when there are disconnects in the timing of reports of PBPK simulations versus the availability of exposure-response information that the clinical consequences are discussed in summary documents such as CTD 2.7.2.. Therefore, the half-sentence in line 462 (e.g. the acceptance limits for a victim drug must be set in 462 perspective of the concentration-effect and concentration-safety relationships of the drug) should be deleted. **Proposed change:** 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.	Partly accepted. Text amended. At the submission of the report there should be a good understanding of the exposure response.
466	2	**Comment:** 'High regulatory impact simulation of a drug as victim of a DDI involving a certain enzyme, the drug model evaluation MAY	Accepted. Text amended.

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		include evaluation…' **Proposed change:** change 'may' to 'needs to or should'. Complex DDI scenario or DDI in special populations not covered. Confidence in the use of PBPK modelling may be low for such scenarios, but they need to be acknowledged.	
469	10	**Comment:** The criteria of diagnostic and acceptance should be separated. Could you give an idea of what the acceptance criteria should be (fold difference…) in case the therapeutic index is relatively large?	Not accepted. Need for a case-by-case assessment stated in guideline.
470-472	10	**Comment:** To be consistent with comment to line 268-274, deletion of the sentence is proposed. Proposed change~~: If the affected enzyme is significantly present in several tissues, such as CYP3A 470 in the intestine and liver, adequate prediction of effects on the investigational drug needs to be shown 471 for inhibition at both locations with satisfactory prediction of Cmax and t1/2 as well as AUC.~~	Accepted. Text amended
472	10	**Comment:** When is a simulation/prediction considered to be "satisfactory"? Please clarify.	Accepted. Text amended
475-476	1	**Comment:** The sentence should be reformulated for clarity.	Partly accepted. Text amended.
475-476	10	**Comment:** meaning of sentence unclear; would the sentence "When assessing the results of the simulation <u>in which</u> the inhibitor used in the study may have affected other proteins (<u>e.g. other CYP enzymes, transporters, etc</u>.) involved in the disposition of the investigational drug, <u>this</u> should be considered." reflect the intended meaning?	Partly accepted. Text amended
483-484	1	**Comment:** Clarifications would be helpful to understand what "demonstrated" means.	Partly accepted. Text amended.
483-484	4	**Comment:** Please clarify what is required as an adequate prediction of absorption. How is adequacy judged?	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
487 and 511-512	10	**Comment:** It should be born in mind that AUC, Cmax, Cmin, are not necessarily regarded as parameters by all modellers. For the pharmacokinetics community, AUC, Cmax and tmax are parameters. To the systems biology community, even terms such as clearance are a function of other more fundamental processes therefore also not necessarily parameters. If one were to be fundamentalist, even a physicochemical parameter such as an octanol-water partition coefficient is but a function of underlying molecular forces and may be predicted, for example, using quantitative structure-activity relationships (QSAR). It is recommended to define what are to be regarded as PBPK parameters, i.e. controlling inputs, as opposed to outputs that can be measured, i.e. metrics, within the context of this guidance and hence for submitted simulation reports.	Not accepted. This level of detail is outside the scope of the current scientific guide.
489	10	**Comment:** Is there no specific expectation regarding descriptive statistics?	Partly accepted, but application specific.
493	4	**Comment:** Please clarify why this list of files is needed as part of the report. Is it adequate to provide the list of files along with the executable file set?	Not accepted. This level of detail is outside the scope of the current scientific guide.
493-495	10	**Comment:** In the case that population files were qualified together with the system and not changed, there is no need to list the population parameters in the simulation report.	Accepted, but there are no current examples.
493-495	10	**Comment:** Result section (5.6) implies that all model parameters should be provided in a tabular format, as well as in an executable format. It is not realistic to extract all the parameters defining population files from commercial software packages into a tabular format. Please consider a tabular format only for key modifications from default population files when commercial software packages were used for PBPK simulations.	Partly accepted. Text amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
497	3	**Comment:** to add **Proposed change:** when the choice is made from a particular set of simulations on only one, a justification on why that simulation was chosen should be provided.	Accepted. Text amended.
499	4	**Comment:** Please clarify which party determines the impact level?	Accepted. Text amended
505-506	4	**Comment:** Please clarify what is envisaged for such a discussion of plausibility.	Accepted. Text amended
508	10	**Comment:** It is proposed to reword the sentence as this seems to be more appropriate. **Proposed change:** …~~ will be~~ are used ~~for the purpose of~~ in this guideline	Accepted. Text amended
513-515	10	**Comment:** More clarity is desirable hence, the proposed rewording **Proposed change:** The structure, ~~i.e.~~ e.g. 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.) ~~and connecting organ blood flows.~~	Partly accepted. Text amended
516	4	**Comment:** Please consider to specify that this refers to "structural" identifiability.	Accepted. Text amended
Section 2	4	**Comment:** We suggest including the following guidance: ICH E11 and concept and reflection paper for paediatrics and also Template for scientific document (part B-E) for application for paediatric investigation plan including deferral and waiver	Partly accepted. Text amended
529	6	**Comment:** "***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*." What constitutes a large	Not accepted. As stated in the guideline, in the context of PBPK models, qualification is purpose and platform version specific. A specific value to define 'large' has not been set.

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		dataset? We feel a reasonable indication of large dataset should be provided.	
532	10	**Proposed change:** Quantitative evaluation of how changes ~~and~~ (e.g. due to uncertainty or variability) in input parameters influence the model output.	Accepted. Text amended
537	10	**Comment:** The true physiological process may never be known. The question is rather: "Does the model describe correctly what is known about the physiological process?"	Partly accepted. Text amended
553	6	**Comment:** Enterocytes is spelt incorrectly	Not accepted.
551	6	**Proposed change:** fm is the fraction of systemic clearance via a certain enzyme (multiple enzymes can contribute to the same pathway but this is not relevant in terms of fm)	Not accepted.