Submission of comments on 'Concept paper on the development of a Guideline on assessment and reporting of mechanistic models used in the context of model informed drug development'

Fields marked with * are mandatory.

* Name of organisation or individual

EFPIA

* Country of organisation or individual

Belgium

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

EFPIA

Please click here to be redirected to the guideline text. The public consultation is launched on 14 February 2025 until 31 May 2025.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section.
If you need more rows to be added to the table, please contact dora.duarte@ema.europa.eu
Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 31 May 2025) by clicking on "Edit contribution" in the link https://ec.europa.eu

/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

EMA Privacy Statement

All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.

This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.

Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller.HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.

For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your personal data for any other purposes outside the scope of this specific context is envisaged.

Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

Publication of data

The following data collected in this questionnaire will be published on the EMA website at the time of issuing the final guideline subject to this survey:

- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

If you complete and submit this survey, your personal data will be kept until the results have been completely analysed and utilised. Your personal data will be deleted by EMA at the latest 5 years after the questionnaire response was submitted. The file of the data as published will remain stored for archiving purposes beyond the maximum 5 years-retention time of the submitted questionnaire responses.

Your rights

You have the right to access and receive a copy of your personal data processed, as well as to request rectification or completion of these data. You may also request erasure of the data or restriction of the processing in accordance with the provisions of Regulation (EU) 2018/1725. You can exercise your rights by sending an e-mail to Datacontroller.HumanMedicines@ema.europa.eu.

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If you have any complaints or concerns about the processing of your personal data, you can contact EMA's Data Protection Officer at dataprotection@ema.europa.eu.

You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu.

* Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
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* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.

- (●) Yes
- ( ) No

Should you not want to give consent to publish, please send your objections to Datacontroller.HumanMedicines@ema.europa.eu.

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency.

For additional information, please consult EMA's privacy statement.

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1. General comments

	General comment
1	It would be helpful for the concept paper to have defined key terms. For instance, what is entailed in “MIDD evidence assessment framework”, to understand how that would relate, or apply, to PBBM models. It makes it difficult to determine if what is meant by some of the terms related to the topics is appropriate for a broad regulatory guidance. In addition, please add an explicit topic on model validation/verification. Maybe this is covered in “model development and evaluation”, but it is not clear that validation would be included.
2	The importance of the “Questions of Interest” as the main guidance for the selection of the appropriate methodology to be used is currently missing (please see and align with ICH M15). Furthermore, guidance to support a better understanding of the risks in the methodology and reliability has to be placed in context of the question being asked. Please link this to the risk qualification of modelling.
3	We would recommend reinforcing the importance of a dynamic model development life-cycle in a predict-learn-confirm paradigm to enable continuous updates of mechanistic models with contemporaneous understanding of the disease and mechanism of action based on the totality of data internal and external to a drug development program. There is no standard approach to mechanistic model development as is the case for population approaches where some standardization is acknowledged by pharmacometricians (e.g., stepwise addition of covariates and subsequent backwards elimination). EMA could provide preliminary guidelines for mechanistic model development and should promote/follow closely the pharmacometrics scientific community on this issue.
4	It is important to provide detailed assessments of mechanistic models used in extrapolation strategies, as model validity and assumptions become more critical and should be rigorously evaluated by regulatory authorities. Additionally, discussing considerations and enablers for the successful application of mechanistic models to translate evidence across populations, diseases, or clinical contexts of use (e.g., transferring learnings regarding optimality of dosage in one rare disease or tumor type in oncology from clinical dose optimization results in a different related indication, bridged via mechanistic models) would be beneficial. Clear guidance on assessing the reliability and limitations of extrapolations to underrepresented populations (e.g., pediatric, elderly, rare diseases) using mechanistic models would also be valuable.

5	Please consider incorporating the following additional aspects in the guidelines: Considerations for handling missing data used in model evaluation. Considerations on integrating and weighing disparate data from diverse sources to reduce inconsistencies in model development and evaluation. Considerations for incorporating real-time clinical data to enable adaptive predictions. Description of models which include empirical and mechanistic features, e.g., a model composed of PBPK to describe PK and an empirical model to describe PD. Quantitative systems toxicology (QST) is an emerging field that has been supported recently by toxicologists. It has profound impact on decision making and MIDD. Please consider including QST to the guideline.
6	Please consider providing additional clarity on the rationale for selecting key criteria used in model evaluation and model assessment, particularly in terms of how these criteria support the model's acceptability and regulatory relevance within the context of its intended use.
7	Clarification is requested regarding the role of this guideline in the context of the draft ICH guideline on General Principles for MIDD (M15) e.g., whether it will be complimentary to and/or address additional aspects of this topic.
8	Please consider including a paragraph discussing the usability of advanced modeling approaches—such as Physiologically-Based Pharmacokinetic (PBPK), Physiologically-Based Biopharmaceutics Modeling (PBBM), Quantitative Systems Pharmacology (QSP), and Quantitative Systems Toxicology (QST)—in the context of the 3Rs (Replacement, Reduction, and Refinement) of animal testing. Emphasize how these models can support or potentially replace animal studies, particularly for complex drug classes like monoclonal antibodies (mAbs), in alignment with the FDA's Roadmap to Reducing Animal Testing in Preclinical Safety Studies.
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2. Specific comments on text

2.1. Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	14-16	Include physicochemical processes in the definition.	Please consider listing 'physicochemical' processes.
2	17-18 and 47	Quantitative systems toxicology (QST) should be included due to its role in de-risking compounds and identifying potential organ toxicity.	Mechanistic models covered by this new guideline include, but are not limited to, Physiologically Based Pharmacokinetic (PBPK), Physiologically Based Biopharmaceutics (PBBM), Quantitative Systems Pharmacology (QSP) and Toxicology (QST) models.
3	23-24	Please clarify the purpose and role of PBBM models in establishing clinically relevant quality limits. In addition, please highlight the interrelationship between PBPK and PBBM models, as PBBM often relies on PBPK outputs.	Suggested language listed below: "PBBM models are a subset or extension of PBPK models that integrates biopharmaceutics principles with physiological data to predict how a drug behaves in the body. PBBM models focus on quantifying the interplay between drug product (DP) quality attributes and how these attributes interact with gastrointestinal physiology. This helps in setting the specification of clinically relevant quality control limits for drug products. Since the relevant readouts for PBBM are derived from PBPK models, it is essential to consider the relationship with PBPK modeling and the importance of evaluating systemic PBPK models for PBBM modeling purposes."

4	25-31	While mechanistic modeling approaches, including QSP, can offer valuable insights into disease trajectory and therapeutic effects, it is important to acknowledge that mapping complex diseases remains aspirational in many cases. Success depends heavily on the availability and quality of data, which can vary significantly between indications (e.g. rare diseases vs COVID-19). Therefore, in addition to the definitional framework for QSP models, the guidance should also recommend a data strategy for building such models—highlighting opportunities, challenges, and the value of open science in sourcing biologically annotated data relevant to disease pathophysiology, mechanism of action, and population variability.	We propose to modify the text from “a modeling approach that is used to map the influence of therapeutic interventions on disease trajectory” to “a modeling approach that attempts to map the influence of therapeutic interventions on disease trajectory. This acknowledges the limitations posed by data availability, particularly in complex or rare diseases and the need for a strategic data framework that leverages biologically annotated inputs and open science practices.”
5	26-27	To integrate a drug into biological systems, time and space are essential to create the biological network.	We would suggest to change the text as follows: “QSP models integrate molecular and cellular mechanisms of the disease and the drug into system-level dynamics at several temporal and spatial scales, thereby providing a bridge between biomarkers and clinical endpoints relevant for the disease.”
6	27-29	Replace “drug” with drug pharmacology. Also, broaden the QSP scope to include models for drug mechanism of action (MoA) in the context of disease biology which is different from those multi-targeted (large scale) platform models addressing the “system-level” or “disease-centric” understanding.	Please consider using "drug pharmacology" instead of “drug”, and broadening the statement here by including fit-for-purpose QSP models which allow for better understanding of drug MoA in the context of disease biology.

7	32-34	Please introduce a QST definition. Also, we would suggest adding Clinical PoC and considering drug interactions for better translational outcomes. Incorporating non-clinical data (e.g., toxicology and the 3Rs) would also support a holistic, innovation-driven modeling approach.	Include definition of QST: “QST models constitute a mechanistic modelling approach that is the integration of classical toxicology with quantitative analysis of large networks of molecular and functional changes occurring across multiple levels of biological organization. A goal of QST is to characterize adverse drug reactions by describing modes of on-target and off-target actions as adverse outcomes pathways and perturbed networks to mitigate risks in drug development processes”. Also, please add clinical proof of concept (PoC), compound interactions. and non-clinical data (e.g., toxicology, 3Rs) to enhance translational relevance in mechanistic modeling.
8	35	Please clarify whether extrapolation refers to a new dosage, or to adapting the existing dosage for special populations (e.g., individuals with renal or hepatic impairment)? In addition, mechanistic models have also been proposed to model surrogate endpoints to inform efficacy and safety.	Please consider including more examples of extrapolation, e.g., for special populations such as those with renal or hepatic impairment. In addition, please add 'adequacy of surrogate endpoints for efficacy and safety'.

9	42-44	To avoid confusion from overlapping guidance (e.g., on PBPK model reporting), it is important to clearly define the specific implementation context for each guideline. In the context of ICH M15, the guidance should also describe the inter-relationships between mechanistic models and other modeling approaches (e.g., pharmacometric exposure–response models) within the broader MIDD framework, to support integrated and consistent evidence generation. Alternatively, consider retiring the guideline with the narrower scope and integrating its content into the one with the broader scope for greater clarity and consistency.	To avoid confusion arising from overlapping PBPK model reporting guidelines, please clearly define the implementation context for each. In alignment with ICH M15, describe how mechanistic and pharmacometric models interrelate to support integrated use within the broader MIDD framework.
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2.2 Problem statement

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	50, 78	It is stated that “Regulators should be able to confidently assess and quantify the potential risks associated with decisions based on mechanistic models…”. However, it should be recognized that some of the uncertainty with respect to mechanistic models is qualitative.	The guidance should recognize the two types of model uncertainty, quantitative and qualitative. It will be helpful to define what is meant by ‘qualitative’ more explicitly. For example, ICH M15 provides a risk assessment framework for model risks, where sponsors have the opportunity to disclose assumptions.
2	53-57	While established PK and PK/PD modeling approaches like PBPK, population PK, and exposure-response analysis have been incorporated into several clinical guidances (e.g., development for pediatric populations, …) with clear recommendations on their use for decision making, this is not the case for QSP. Consequently, a major reason for the underuse or inappropriate use of QSP in regulatory interactions is the missing link to guidance for medicine development that highlight the value of this tool.	Please consider adding examples of potential applications for appropriate QSP model submissions.
3	61	The draft concept paper refers to structure “identifiability” and does not mention “verification” or “validation”. The draft ICH M15 on MIDD does not explicitly mention model identifiability but does discuss “model evaluation” in section 3, including elements on verification, validation and applicability assessment.	Clarification may be provided as to whether model /structure “identifiability” in this concept paper is fully reflected in “model evaluation” in the draft ICH M15 guideline or if the concept paper is emphasizing a different consideration via model/structure “identifiability”. This will ensure consistent use of /understanding of terminology as well as expectations as regards evidential requirements for model identifiability, including that required to be submitted to EMA.

4	61	Checking structure identifiability might be hard for all mechanistic models and it is not necessarily part of the modelling framework (in particular for highly mechanistic QSP models). Although parameter identifiability can be very important, QSP approaches are also used for hypothesis testing and the creation of clinical case scenarios and model calibration and validation are often done with very limited data which makes hard any kind of parameter identifiability analysis. However, model parameter ranges need to be checked to see if they are plausible and physiologically relevant (as mentioned in the following bullet point of this section).	We would suggest to provide guidance on requirements including illustrative examples and the conduct of identifiability analysis with clarity on which scenario identifiability is definitively needed and in which scenario it can be excluded with proper justification.
5	63	"biological" plausibility	"Mechanistic justification and biological plausibility of model structure and parameters"
6	63	Conceptual knowledge and biological understanding is NOT sufficient to justify model structure / topology etc. That should be combined with in-depth scientific review of relevant data to justify technical feasibility of the development plan.	Model structure/topology should be justified not just by biological understanding, but also by thorough review of relevant data to ensure technical feasibility.
7	63-65	Bullet points under lines 63-64-65 should be combined.	Please consider combining bullet points under lines 63-64-65.

8	66	The addition of "quantification" emphasizes the need for a precise and systematic measurement of uncertainty, ensuring that it is not just acknowledged but rigorously evaluated. Including "variability" highlights the importance of recognizing and accounting for differences and fluctuations in data from various sources, which can significantly impact model predictive performance.	"Data from different sources are used to inform parameter values: propagation and quantification of the uncertainty related to their quality and variability and relevance on model predictive performance should be considered (i.e. uncertainty quantification)."
9	66	Variability and uncertainty are used interchangeably but they are not exactly the same. Back in 2021 there was a special working group from ISoP QSP SIG to address communication gaps in this terminology. A key outcome was the recognition that variability and uncertainty are distinct concepts. Specifically, variability refers to population heterogeneity and it is irreducible by additional data while uncertainty refers to lack of knowledge / data and therefore can be reduced by additional measurements. In this context, variability can be addressed by virtual population analysis while propagation of uncertainty is quantified by other advanced tools and statistical methodologies.	"Data from different sources are used to inform parameter values and population heterogeneity: beyond variability analysis that can be addressed by virtual population algorithms, propagation and quantification of the uncertainty related to robustness of model predictive performance should also be considered."
10	70	The draft concept paper states that relevance of the available data for model evaluation is particularly important. However, clarification is requested as to whether the use of evaluation relates to model verification or validation or both.	Please clarify whether the evaluation relates to model verification or validation or both.

11	72-73	Vpop and digital twins are not the same methodologies - the guidelines should clarify nomenclature and be consistent throughout the document. A digital twin is closer to a "virtual patient" as it is considered to be a model parameterization used to evaluate an individual response. Virtual populations are designed to evaluate the behavior and interindividual variability in a specific population.	The generation of virtual populations as well as the use of virtual twins should be explained and correspond to the intended use.
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2.3 Discussion (on the problem statement)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	75-83	PBPK/PBBM modeling has clear and specific applications with a focus on pharmacokinetics advice. QSP combines and leverages modeling aspects and techniques from various approaches.	For QSP, we would recommend including cross-references to other modeling approaches and their respective guidance such as exposure-response analysis, PBPK, biostatistics, or real-world evidence. We would recommend highlighting the synergies and conflicts between approaches to facilitate their integration into a QSP model. This should reduce ambiguity around QSP submissions.
2	76-83	Model and assumptions are particularly significant for the model outcomes; thus, their validity and impact should be discussed.	Please consider adding: Validity of assumptions and impact of the utilization of mechanistic models on extrapolation strategies.
3	75	There may be specific needs for model evaluation and uncertainty qualification in specific areas e.g., for paediatric applications. It would be helpful to provide guidance on these specific needs.	Please provide additional information on what specific needs should be considered for specific areas.

4	76	QSP models can be 'fit for purpose' models i.e., describing cell mechanisms linking a specific target to a set of clinical biomarkers or 'platforms model' i.e., a framework trying to capture as much biological complexity as possible in a specific disease indication. Platform models can be used for multiple purposes to address specific questions, however their qualification is challenging. Furthermore, commercial platforms often do not disclose all the physiological information used in their model framework or the sources for parameterization. Additionally, the full model structure may be partially or fully hidden.	Please describe what documentation is expected to support model structure, relevance and validation that supports their qualification.
5	77	Regarding application of the MIDD evidence assessment framework on mechanistic models, it will be good to give detailed illustration of case studies to show application.	Please provide case studies of the application of the MIDD evidence assessment framework on mechanistic models for illustration.
6	78	Uncertainty Quantification (UQ) could include UQ on parameter and output/prediction, and these could be very different. Certain model output/prediction could still be constrained well and robust, even if some parameters are loosely constrained or unidentified, given the sloppy nature of mechanistic models. In practice, it is the relevant prediction that is of more importance to clinical decision-making.	We would suggest including in the guideline: "In practice, uncertainty quantification on model output /prediction should outweigh uncertainty quantification on parameters."

7	78	The concept paper refers to “uncertainty quantification” and also cites the ICH M15 draft guideline on MIDD. However, the latter does not refer to this term although it does refer to “uncertainty (e.g. sensitivity analysis)”. As such, clarification is requested as to whether “uncertainty quantification” is intended to have the same meaning as sensitivity analysis or if the concept paper is emphasizing a different consideration.	Please clarify the definition of Uncertainty Quantification.
8	79	It is unclear whether the identifiability mentioned in this bullet point "Model structure and identifiability." refers to model structure or model parameters.	We would suggest revising this bullet point ("Model structure and identifiability.") to: "Model structure justification and model parameter identifiability analysis.", to ensure the guideline addresses key sources of uncertainty from both model structure (model topology) and parameter identification.
9	79	"Model structure and identifiability": While identifiability certainly matters for QSP models it is often assessed by whether the QSP model can generate consistent and reproducible predictions across relevant scenarios. QSP models can show uncertainty in certain parameters but still produce robust model outputs.	We would recommend including clarity on model structure and identifiability in the context of the relevance of the model for the intended purpose.
10	79	Regarding model structure and identifiability, we would suggest using the term ‘parameter identifiability’ as individual parameters are subjected to identifiability analysis.	We would suggest using "parameter identifiability" as a better term in the context of this document.
11	80	Please consider adding guidance/regulatory expectations for submission of relevant datasets and model codes and whether this becomes relevant from a regulatory perspective.	Please consider adding guidance/ regulatory expectations for submission of relevant datasets and model codes.

12	80	Often data is collected from literature which can introduce bias. The fact that there is reliance on the value because it is published must be recognized. There is no way to check it for fidelity.	Please clarify in the text the utility of literature data and the expected “validation or sensitivity analysis of that data”.
13	81	The difference between model structure and model development is unclear.	Please combine model structure and parameterization into one topic, and model evaluation and application into another.
14	81	"Model development and evaluation": The scope of this element would benefit from further specificity. While ICH M15 specifically discusses verification, validation and applicability evaluations as part of model development, details regarding the building of risk-informed credibility into a model is absent.	We would recommend discussing the reporting framework for model calibration and validation that establishes risk-informed model credibility.
15	83	A recent publication of a paper on “Development of a Physiologically Based Biopharmaceutics Model Template: Considerations for Improved Quality in View of Regulatory Submissions” may serve as input and reference for “best practices on reporting”.	Please consider adding the following as a reference: https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.5c00225
16	83	Reporting of results can be context- and model-dependent including the use of AI/ML in mechanistic modeling.	We would suggest the guideline distinguishes between the reporting of model building results (calibration), model validation and model application (prediction case studies) and clearly states expectations.

17	83	Three relevant aspects defined in section “Problem statement” are not included in this section i.e. bullets 2, 3 & 5. Bullet 3 (“Assumptions made related to model structure and parameters need to be justified”) is critical and sensitivity analyses assessing impact of deviations from the assumptions should be part of the exercise.	Please discuss aspects noted to align with the Problem Statement: • Mechanistic justification and plausibility of model structure and parameters. • Model structure assumptions and parameters made especially sensitivity analysis. • Assessment of model predictive performance in the context of its intended use of model.
18	83	In addition to best practices for reporting results, it is recommended that the guideline also addresses best practices for clearly communicating the content /structure of the models and how they were developed.	Please include information on the expectations for clearly communicating the content/structure of the models and how they were developed.
19	83	A valuable addition is addressing how to validate the different mechanistic models. From a statistical perspective, validation is done by using observed data and comparing them to the predictions made by the models (learn/confirm paradigm). Similarly, validation could be approached from an intrinsic scientific /biological perspective.	Please consider adding a discussion on the statistical and intrinsic validation of mechanistic models.
20	83	A valuable addition would be a section on the importance of clearly defining the data source. This could address experimental data points, parameter values that are being used (not estimated), whether all potential sources for the parameter value are taken into account, a clear rationale for when the value is taken from one source and others are not taken into account, etc.	Please consider adding a discussion around the importance of defining data sources including experimental data points and parameter values. This could include the role of Bayesian methods in building and applying priors and providing a statistical framework for using real world evidence in regulatory decision making.
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2.4 Recommendation

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	85	Please consider clearly stating the requirements for model submission to meet reproducibility of model building and simulations.	“.... recommends drafting a guideline on submission requirements, assessment and reporting ...”
2	85-87	Different mechanistic modelling approaches (PBPK, QSP, PBBM) have different remits, applications and focus areas. This might need a differential approach on validation requirements for them. Could the document include how this will be handled in one guidance document?	We would suggest to add an appendix to the guideline to highlight specific validation requirements for the different modelling approaches.
3	85-87	It will be helpful to provide case studies for each mechanistic modelling approach to show how uncertainty quantification, and structure identifiability can be handled.	Add the following text: “The guideline will notably contain case studies for each mechanistic modelling approach to show how uncertainty quantification and structure identifiability can be handled.”
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2.5 Proposed timetable

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
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2.6 Resource requirements for preparation

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	92	Suggest including clarification of which skills groups (apart from clinical experts) will be in the core drafting group and the wider group of contributors. In the Introduction, PBBM is highlighted as being the interplay between drug product quality attributes and specifications. The build of the model and the use in a quality perspective needs to be combined. As such, consideration should be given to including a quality and pharmaceutical expert with knowledge of topics such as dissolution. It is also recommended that an expert with a technical profile with a deep understanding of both pharmacology and its mechanistic models as well as statistics be included.	Please consider the following suggestion: “The core drafting group will be a writing team of 4-6 people including clinical experts, technical experts with extensive knowledge of both pharmacology and its mechanistic models, biostatisticians as well as quality /pharmaceutical experts.”
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2.7 Impact assessment (anticipated)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
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2.8 Interested parties

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	110	Other Agencies and groups of stakeholders should be considered, such as ANVISA and ICH.	"The Guideline will also benefit from the input of other regulatory agencies (e.g. FDA, PMDA, HC, ANVISA, ICH, CDE)"
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2.9 References to literature, guidelines, etc.

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
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Thank you for your contribution.

Contact

Contact Form