EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
An agency of the European Union

12 March 2025
EMA/91404/2025

Overview of comments received on ICH M15 Guideline on general principles for model informed drug development (EMA/CHMP/ICH/496426/2024)

Please note that comments will be sent to the ICH M15 EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Pharmetheus	0			Pharmetheus welcomes the guidance on the General Principles for Model-Informed Drug Development (MIDD) and considers it as a significant milestone in harmonizing regulatory decision-making and promoting the broader adoption of MIDD approaches. The guidance would benefit from including case examples, such as a populated "Table for Assessment of MIDD Evidence" in Appendix 1, to better illustrate the practical application of the assessment table. Additionally, the intended use of this table remains unclear, particularly regarding its role across the sequence from "planning and regulatory interaction to implementation, reporting, and submission". Should it be integrated into relevant analysis plans and reports, or should it serve as a stand-alone document to support a specific claim or MIDD application? Providing case examples on the intended use throughout drug development and regulatory interactions would offer further clarity.	
Pharmetheus	0			To ensure clarity, we recommend using consistent definitions throughout the document and aligning them with relevant regulatory guidelines, particularly ICH E9, for terms like model risk, model impact, assessment, acceptability, applicability, appropriateness, and evaluation.	
Medicines for Europe	0	0	0	No requirements in the traceability of the clinical data from studies to MIDD models is stated in the guideline.	
Medicines for Europe	0	0	0	No Data transfer requirements are clearly stated in the present guideline for authorities' submission. CDISC standards are expected in the submission to authorities of the MAR?	
Medicines for Europe	0	0	0	No responsibilities structure is specified in the present guideline. Is the MIDD expected to have a specific responsible investigator to coordinate the preparation of the related documents (i.e. MAP, MAR, etc.) and the training matrix of the involved personnel?	
Parexel	0	0		As the Question of Interest may be broader than a single MIDD approach, the word "address" might be more appropriate than "answer" in this context. We suggest to change from "answer" to "address" throughout the guidance when referring to the Question of Interest.	
Parexel	0	0		It might be beneficial to the reader if examples can be given to illustrate definitions, or specifications that are requested to be provided which would make the reading more comprehensive.	
Teva Pharmaceutical Industries Ltd.	0	0	0	It would be helpful if this ICH guideline provided detailed elaboration on the use of MIDD in specific therapeutic contexts, such as pediatrics, new indications based on similarities, and others.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Teva Pharmaceutical Industries Ltd.	0	0	0	It would be beneficial for this guideline to elaborate on the use of MIDD in specific techniques, such as extrapolation methods, utilizing data from other molecules, incorporating historical data, and real-world evidence, among others.	
Teva Pharmaceutical Industries Ltd.	0	0	0	As this guidance focuses on the assessment of MIDD evidence, rather than the technical aspects of model development, it would be beneficial to plan to issue additional guidelines and/or a Question and Answer (Q&A) document to be read in conjunction with this guidance.	
Amsterdam UMC, Imke Bartelink & Niels Vermeer	0	0		WE highly welcome the current guideline of MIDD in clinical drug development.We feel that to maximalize its impact on the to be licensed dose, MIDD should be an intregal part of the investigational brochure and / or clinical trial applications under the ECTR. this should inform the decision of the first in human dose and be updated troughout the course fo phase 1-3 clinical studies.	Exposure /biomarker response and covariate analyses on PK and PD should be used to inform and individualize the absolulte dose and the dosing intervals at treatment onset and upon response during maintance treatment.
Teva Pharmaceutical Industries Ltd.	196	198	4.3	*"Additional details should be provided in meeting background materials or Common Technical Document sections, with cross-references to source documentation"* . It is suggested that some details regarding the meeting be included. Specifically: is this meeting intended for MIDD; how is meeting requested; what should be covered in the scope of the request and the meeting backround; what format should the meeting follow?	
Medicines for Europe	0	0	0	We appreciate the general guidance in the documents and also that it does not include details regarding technical aspects and focused on key assessments. The guidance refers to rate Model Risk and Model Impact as low, medium or high and recognize that this may vary case by case (line 84). However, it would help if the guidance would provide more insight on how regulators would expect sponsors to justify their ratings as either low, medium or high (line 75 – 83) and how regulatory authorities will assess them.	Suggestion to add more insights on how to justify ratings of low, medium or high and how regulatory assessment will assess them.
EFPIA	General	General		The guidance is currently very general - examples would be extremely valuable to include as part of the planned training materials	
EFPIA	General	General		Engagement with regulators mentioned throughout the document. Could reference be provided (region specific examples) on how to initiate this	Include reference to details on how to initiate engagement
EFPIA	General	General		Consider alignment with draft guidance for use of AI - https://www.fda.gov/media/184830/download.	Further consistency in terminology outlined in other guidance documents which fall into scope of ICH M15
EFPIA	General	General		Prospective planning of analyses (before the data are available) are crucial to ensure reliability of findings [1-3]. The guideline emphasizes the need for planning (via assessment table & MAP), but it remains unclear how „prospective" this planning needs to be. Is it enough to finalize assessment table & MAP before analysis start (which may be after data-base lock of the main data source(s) and thus not truly prospective)? How to prevent that assessment table and MAP are filled out after the analysis has been completed? [1]Ioannidis, J.P.A. (2005). "Why Most Published Research Findings Are False." PLOS Medicine. [2]Simmons, J.P., Nelson, L.D., & Simonsohn, U. (2011). "False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant." Psychological Science. [3]Gelman, A., & Loken, E. (2013). "The garden of forking paths: Why multiple comparisons can be a problem, even when there is no 'fishing expedition' or 'p-hacking' and the research hypothesis was posited ahead of time."	More clarity should be provided on when assessment table & MAP need to (provably) finalized. Consequences of failure to create a prospective assessment table and MAP, should be mentioned more clearly.
EFPIA	General	General		The guideline suggests that initial interactions with regulatory agencies should take place through the MAP, followed by the submission of relevant MARs during the evidence submission phase. However, it is not unusual for sponsors to submit a detailed report that consolidates both the MAP and MARs into a single document. The regulatory interaction approach should remain adaptable, depending on the stage of drug development and the influence of the model.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	General	General			Please provide examples in training materials to help interpret the guidance further.
EFPIA	General	General		There are many platforms/technical aspects of MIDD. We would suggest providing examples (e.g. in the appendix or the supplementary learning material that usually follows finalization of the ICH guidance).	Provide more clarity through use of examples, particularly for the Key Assessment Elements (Section 2.1) additionally, for example, what is meant by model risk being high, medium, low; criteria of model performance 'by graphical and numerical approaches'?
EFPIA	General	General		General comment: The guidance refers to a wide range of models and provides high-level recommendations. Please consider including some examples as they will be helpful to interpret the guidance.	
EFPIA	General	General		It is acknowledged that the scope of MIDD is quite extensive, and the guideline must maintain a higher-level perspective to encompass various modeling and simulation (M&S) methods. However, in this approach, the current draft lacks specific examples of how to apply the guideline effectively. The guideline would greatly benefit from including tangible examples of its application for specific M&S methods, such as PBPK, PBBM, and Pop PK. These examples could be included as an appendix to the guideline.	
EFPIA	General	General		The guideline outlines Model Risk as low medium and high. Industry would benefit if some examples for each category could be added to follow the regulatory thinking.	
EFPIA	General	General		It is considered helpful to have an appendix fopcusing on and providing example assessment tables for MIDD planning and submission stages explaining how the concepts of this guidance are applied. This can be based on generic or real cases and will provide further clarity and contribute to harmonization in the implementation of this guidance.	
EFPIA	General	General		The guidance requires the rating of Model Risk, Model Influence, Consequences of Incorrect Decisions, and Regulatory Impact on a scale of low, medium, or high. However, it lacks clear definitions for these rating levels in the draft, making it challenging to apply them consistently. Establishing a clear framework or standards for these ratings would aid in their uniform implementation. Additonally, the guidance does not specify how these ratings influence regulatory alignment or interactions, nor does it clarify if the rigor of model evaluation remains consistent across different rating levels. While the guidance advocates for early regulatory engagement for novel modeling and simulation methods or when Model Risk and/or Model Impact are high, it does not address the necessity of such engagement when all ratings are low. Furthermore, it suggests that Model Evaluation should align with the level of Model Risk, but it remains vague on whether certain evaluation steps might be omitted to improve efficiency for models deemed low risk.	1) Inclusion of Examples and Case Studies: It is advised to include examples or case studies that demonstrate how to define and apply rating levels for the various categories, as well as the expected outcomes. For example the Model Risk Matrix (Figure 2) illustrated by Kuemmel, C., et al., in their development of a risk-informed credibility assessment framework for PBPK modeling and simulation could serve as a valuable example. This would help stakeholders better understand and implement the guidance effectively. 2) Flexibility in Regulatory Interactions and Model Evaluations: It is recommended to introduce more flexibility regarding regulatory interactions and model evaluations. This change would allow adaptations based on specific circumstances and the risk levels identified, facilitating a more tailored and efficient regulatory approach. [Reference: Kuemmel, C.,et al. (2020), CPT Pharmacometrics Syst Pharmacol, 9(1), 21-28. doi:10.1002/psp4.12479]
EFPIA	General	General		The document should be consistent if the intention is that MIDD evidence "may contribute to" the answer to Questions of Interest or directly answer the QoI. This is framed differently in different parts of the draft (e.g. 1.4 and 2.1).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	General	General		Key assessment elements should be part of MIDD planning stage along with Appropriateness of Proposed MIDD and Technical criteria. This should be combined under one section 'MIDD planning and regulatory interaction'.	
EFPIA	General	General		Bayeisan Emax modeling has been designated fit-for-purpose under a few conditions by FDA in an integrated review performed in 2021 (link: https://www.fda.gov/media/160981/download). This methodology supports model-based dose finding at the clinical and preclinical stages of drug development, and can greatly inform decision making around choosing the optimal dose, and which doses should or should not be explored in future drug development.	Sponsor recommends inclusion of this modeling methodology in the updated guidance.
EFPIA	General	General		For Regulatory review, agencies need to ensure appropriate file types are included in their specific eCTD for appropriate download and review.	
EFPIA	General	General		The ICH M15 guideline is a welcome addition. However, it seems to emphasize more on the formality, and no mention on the practical benefits of using MIDD for drug development and regulatory decisions.	The guideline should include high-level descriptions of key Questions of Interest that MIDD can answer by MIDD and its potential impact. This is important to enhance the MIDD utility, especially for newcomers. Additionally, developing case examples in future training materials would be beneficial. Summary of the
EFPIA	General	General		There is much recommendation on regulatory interaction.	Suggest adding recommendations for regulatoy interactions at MIDD planning and submission stages, and potential interative process
EFPIA	General	General		The guideline recommends obtaining scientific advice from regulatory authorities on the MIDD strategy. Has a combined review across agencies been considered to ensure a more efficient review and reduce Industry filing burden?	
EFPIA	General	General		Scope of this draft guideline on AI/ML: In the guideline, AI/ML is cited as an example of modeling and simulation, and MIDD is very broadly defined as "the strategic use of computational modeling and simulation (M&S) methods that integrate nonclinical and clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence." There is no limitation regarding the specific uses of AL/ML in drug development in this guideline. AL/ML can have very broad applications in drug development spanning discovery, pre-clinical research, clinical research, manufacturing, and post-authorization. The guideline should clearly state the specific requirements in the guideline, such as MAP/MAR and risk rating of low/medium/high, are applicable to all AL/ML applications that meet the definition of MIDD, regardless their Context of Use, if this is the intention of the guideline. There is no formal guidance from FDA or EMA on the application AL/ML in drug development; therefore, it is not clear if FDA or EMA will recognize the approach proposed in this guideline regarding AI/ML.	
EFPIA	General	General		Many of the terms and ideas in this guidance seem to relate to the ASME V&V 40 standard (V V 40-2018) for computer modeling & simulation but some of the terms and definitions are different in the guidance than the standard and the V&V 40 standard is not called out as a reference. Using different terms could cause some confusion as the standard would likely be leveraged in many/most countries in the development of models. The FDA additionally has a CM&S guidance that references the V&V 40: https://www.fda.gov/media/154985/download. The ICH guidance is focused on more than the US, but the current standard and guidance should be considered in overall harmonization.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	General	General		V&V 40 standard (ASME V V 40-2018) should be included as a reference document in the guidance as this standard will likely be used in the development of a model.	Reference ASME V V 40-2018
EFPIA	General	General	Title	The title suggests a broader content/scope than the actual document in my opinion. The guideline focuses on providing a framework for "assessment and documentation" of MIDD evidence to inform decision-making & communication with agencies. It does not -as specifically mentioned- includes details regarding technical aspects (in contrast to the first draft) which arguably could be expected from the title.	General Principles Framework for assessment of Model-Informed Drug Development
EFPIA	General	General	1.1	It would be helpful to highlight in the Objectives that this harmonized guideline is intended to drive increased standardization in MIDD practices, clarity and consistency in regulatory decisions related to MIDD, and greater awareness and acceptance of these practices.	
EFPIA	General	General	1.2	Including a high level summary on the key Questions of Interest in the background section is recommended.	
EFPIA	General	General	Appendix 1	Key assessment elements should be included at the MIDD planning stage. Currently, the way the table has been listed gives the impression that at MIDD planning stage, only Appropriateness of Proposed MIDD and Technical Criteria for model evaluation and model outcomes is required. This has been clearly mentioned in Table 1 that the key assessment elements and additional information are part of planning and regulatory interaction.	Sugget Appendix 1 be harmonized with Table 1.
EFPIA	General	General	Table 1	Technical criteria of model evaluation and model outcomes – it is not clear what the guideline means here whether sponsor need to set different criteria for model evaluation and model outcomes. On the other hand, model evaluation includes verification, validation and applicability assessment. Model outcomes are usually the simulated profiles or parameters from the model. Validation usually means (for PopPK, PBPK, PBBM) assessment of the model performance in comparison with relevant observed in vivo data where comparison with observed data which inherently compares model outcome to observed data. Thus, the distinction between model evaluation and model outcomes and setting technical criteria for each is not clear.	request clarity on the distinction between setting technical criteria for model evaluation and for model outcomes. +A47:G56

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	5	6		It is mentioned 'It establishes a harmonized assessment framework (including associated terminology) for MIDD evidence'. The guideline also provides recommendations on regulatory interactions, so the above statement should be broadened.	"It establishes a harmonized assessment framework (including associated terminology) for MIDD evidence and recommendations for regulatory interactions."
Pharmetheus	8	10	1.2	The definition of MIDD suggests that it requires the integration of both non-clinical and clinical data, along with other quantitative or qualitative knowledge, for its application	"MIDD is defined as the strategic use of computational modeling and simulation (M&S) methods that integrate nonclinical **and/or** clinical data, prior information, **and/or** knowledge (e.g., drug and disease characteristics) to generate evidence."
EFPIA	8	10	1.2	Change to 'and/or' when discussing integration of data for M&S.	... methods that integrate nonclinical and/or clinical data, prior information and knowledge...'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	13			One of the main concerns is the lumping of all modeling methods together and treating them similarly in terms of MAP and MAR templates and model evaluation, regardless of the maturity level of each modeling approach. This approach can be problematic because different modeling aspects, such as MAP & MAR, have varying levels of complexity and maturity, which necessitate tailored evaluation and handling procedures.	Consider a tailored approach to evaluating and handling procedures for different modeling aspects with varying levels of complexity and maturity.
EFPIA	13			The last bullet "AI/ML" is a bit out of place in this list as it refers to set of methods, while all other refer to a specific area of applications. AI/ML could in principle be used in any of these (e.g. pop PK). The authors seem to explicitly mention AI/ML.	Replacing line 13 "methods" with "applications" and exclude AI/ML from the list. Instead add: The methods using in MIDD M&S include but are not limited to: - mixed models - Bayesian methods - AI/ML Note: on line 23-24 the phrase "M&S methods and applications" is used
EFPIA	13	21	1.2	Suggest including clinical trial simulations as an example of MIDD approach. Additionally, consider updating bullet in Line 21 to "Artifical Intelligence/ Machine Learning models"	
EFPIA	13	21	1.2	Current list is a combination of both model types/methods and applications of model types/methods e.g Disease progression models could also be QSP models, QSP models could be agent based models etc. QSP models could also be ordinary differential equations, partial differential equations etc but these are not listed as methods.	Decide whether list should comprise model types or application areas or model methods and revise (and update text on line 13 accordingly). Propose to switch wording to applications - i.e remove agent based models and AI/ML (and replace with specific applications)
EFPIA	13	21	1.2	Does the inclusion of machine learning in this list intentionally bring QSAR models into scope? Already covered with QMRF guidance.	Consider alignment with existing guidance if so
EFPIA	13	21		Artificial intelligence/machine learning is applicable to almost all the previous points and is not a specific modeling method.	
EFPIA	13	21	1.2	A list of examples are given as to what is included in the term M&S methods. It is clearly stated that it is not a complete list however I think that pharmacodynamics should be mentioned since this is central to many things we do, in addition to PK and ER.	Add a bullet point: Population PKPD
EFPIA	14			"Pharmacodynamics" should be added to "Population pharmacokinetics".	Population pharmacokinetics and pharmacodynamics
Parexel	16	16	1.2	Please consider changing "Dose-exposure-response" to "Integrated Dose-exposure-response analyses".	
EFPIA	16	16	1.2	Dose-exposure-response is a bit confusing as they are two separate analyses (dose-response and exposure-response)	Suggest splitting it into two bullets: - Dose-response - Exposure-response
EFPIA	21	21	1.2	AI/ML is a very broad class of models compared to the other approaches that are listed (e.g. Population PK).	suggest to delete it from this bullet list and e.g. clarify in footnote 2 above that modeling may also utilize AI/ML methods.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	21	21	1.2	Formal validation and verification processes for Artificial Intelligence (AI) methodologies are immature and likely lack sufficient, realworld regulatory experience, relative to the other listed M&S methods that are in-scope for this guidance. Foundational AI models may also be licensed from third-party vendors without full documentation, explainability, or reproducibility (across the time frame of the MIDD submission) that are generally expected of the other listed methods.	Suggest that AI be removed as an M&S method, with perhaps a footnote to explain how sponsors should approach MIDD submissions containing such methods with caution and transparency. Further suggest that Machine Learning remain as in-scope, as these methods are often fully describable with underlying data and code.
EFPIA	23	31	1.3	It is unclear whether is it recommended to use the assessment table comprehensively for any modeling work to be submitted to a regulatory agency (for example, for a routine Pop PK assessment included in a WMA filing), or for seeking scientific advice or otherwise trying to communicate with an agency about specific modeling-related questions or to support more novel applications of MIDD	Please clarify
EFPIA	23	31	1.3	There is an emphasis on clinical applications of MIDD throughout the document - inherent in the definitions of consequence of wrong decision for example. This may automatically put a ceiling for scores for non-clinical applications at low/medium. To consider making clear that the guidance is by first intent for clinical applications or consider broadening scope and definitions to include non-clinical applications	Consider changes to either clarify focus of document by first intent is for clinical modelling and simulation approaches or expand scope and revise definitions to include non-clinical scenarios
EFPIA	24	25	1.3	Add that it is expected that the guideline is used for any relulatory interactions when MIDD is used	"provides recommendations for any related regulatory interactions, reporting, and submission"
EFPIA	27	28		ICH M13A should also be referenced as it refers to PBPK.	Add in ICH M13A as this also refers to PBPK This guideline is intended to facilitate a multidisciplinary understanding of MIDD and associated evidence generation. It should be used in conjunction with relevant topic-specific ICH guidelines (e.g., E4, E5, E6, E7, S7B, 27 E11[R1]/E11A, E14, M12, M13A, E17, and E9/E9[R1])
EFPIA	29			The guideline is too general, not providing enough detailed instructions for different types of models and their specific requirements.	
EFPIA	29	30		The term ‘Model development’ has been mentioned in the lines, however, no definition of this term is provided in the glossary.	Suggests including: “Model Development focuses on the model’s conceptual form (i.e., overall structure and complexity), the model assumptions and the approach to generation of input data and model parameterization.”
EFPIA	31	31	1.3	Reference to appropriate 'accepted standards' would be helpful	Consider adding refernces to existing standards (recognising these may need to be regional examples of guidances which are reviewed and updated so not to be outdated)
EFPIA	31	31	1.3	References are needed with the 'current accepted standards and/or scientific practices for the M&S method(s).'	Please provide proper guidance or reference
EFPIA	34	36	1.4	The sentence "...When MIDD" is not clear.	When MIDD evidence contribute, then it is key to identify Questions of Interest that are informed by MIDD early, such that appropriate data generating activities can be incorporated into the overall drug development plan.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	34	35	1.4	Simplify sentence.	"When MIDD evidence can help answer Questions of Interest, early planning ensures that the necessary data is included in the overall drug development plan."
EFPIA	35			In "early planning allows the data to be generated ...", suggest to further clarify what "data" refers to here: is it input data (for modeling) generated in early trials, or result data/outcomes generated by early modeling?	Requests clarification of “data” in the context of “early planning allows the data to be generated…”
EFPIA	35	35	1.4	For clarity of the sentence, rephrase "allows the data to be generated to be incorporated into the overall drug"	"allows the data to be generated and incorporated into the overall drug"
EFPIA	40	41	1.1	For clarity of the sentence "its use across the sequence of “planning and regulatory interaction” through to “implementation, reporting, and submission.”, suggest to discard the term through	
EFPIA	41	43		This sequence is split into five distinct activities. The link between these activities and the relevant guideline sections and subsections is provided in the guideline overview (Table 1). To improve the structure and the readability of the guideline, it could be considered to make these 5 (consecutive) activities the main chapters of the guideline.	Suggestions: Section 1: Key assessment elements Section 2: Additional considerations to inform decision making Section 3: Model evaluation Etc.
EFPIA	47		Table 1 Section 2.1	The current list under "Key Assessment Elements" does not reflect the detailed explanation in Section 2.1. More specifically, Model Influence and Consequence of Wrong Decision should be within the Model Risk consideration.	Suggestion to aligning Table 1 “Key Assessment Elements” with information included in Section 2.1.
EFPIA	47		Table 1	MIDD is a general framework and not a sequence (which refers to specific activities), so there seems to be missing a noun in the table title	Suggestion to update the Table 1 title to “Guideline Overview: Sequence of MIDD activities in Relation to the Relevant Guideline Sections”
EFPIA	47	48	Table 1	Minor: the order of the Key Assessment Elements could be refined to reflecting the elements from the models to broader impact.	Suggest moving Model Risk before Consequence of Wrong Decision. Also, in later sections.
EFPIA	47	48	Table 1	The terms of Model Influence and Model Impact in Key Assessment Elements are too similar.	Suggest rewording Model Influence to Weight of MIDD or somehting more apparent.
EFPIA	47	48	Table 1	Key Assessment Elements: Consequence of Wrong Decision is part of Model Risk and does not need to be listed separately	Suggest deleting Consequence of Wrong Decision from Key Assessment Elements column
EFPIA	47	48	Table 1	Documentation for Regulatory Interactions and Submission: Key components such as datasets, relevant model files and outputs are not listed	Suggest including key information such as datasets, relevant model files and outputs within Documentation for Regulatory Interaction and Submission column
EFPIA	47	47	Table 1	Text in 1.4 says activities described in the document may be in parallel/out of order but in Table 1, the table heading mentions 'Sequence of Activities' which could be considered contradictory to the messaging in the text	Replace 'Sequence of Activities' with 'Activities' in Table 1 heading
EFPIA	47			See table caption suggestion in column F. Should model assumptions and uncertainty be specifically called out in the table under model evaluation/validation since these are important to be considered?	Guideline Overview: Sequence of MIDD Activities in Relation to the Relevant Guideline Sections

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	49		Section 2	Section 2: In the Background (Section 1.2), evidence is defined as model + data + prior knowledge and information. In Section 2, the evidence assessment focuses primarily on the impact of the model (e.g., Model Influence, Model Risk, Model Impact). While models are a key element of MIDD Evidence, the data and knowledge/prior information are also important and should be explicitly part of the assessment elements.	
EFPIA	49	59	2	Suggest to add further guidance on the timing of when the assessment is expected.	
EFPIA	50			To better clarify the type of evidence assessment, suggest explicitly identifying risk and impact assessments in the first sentence.	Suggestion: This section describes key concepts for assessing the impact and risk of using MIDD evidence to inform decision-making.
EFPIA	53	56	2	It would be helpful to clarify regulatory expectations on when to seek alignment and feedback (e.g at planning and/or submission stage and/or any time where new information or data arise). As the guidance states, MIDD is iterative and objectives and modeling and simulation approaches may evolve during drug development. In the context of this clarification of when to seek alignment and feedback from regulators, distinguishing between commonly accepted approaches, e.g. population PK or exposure-response analysis, and more novel MIDD approaches will also be helpful.	Drug developers should may use the assessment table as a tool for communication within and between drug developers and regulatory authorities across multidisciplinary teams to increase transparency and provide an understanding of MIDD in the course of development (i.e at the planning stage, submission stage or at any time needed in the course of development). Early alignment with regulatory authorities facilitates subsequent acceptance of MIDD evidence, especially when using complex or new approaches.
EFPIA	55		Section 2.2	Based on Section 2.2 (Considerations for Interaction with Regulators), it seems that these assessments should be provided at both the MIDD Planning and Evidence Submission stages, not just the planning stage. Suggest clarifying this sentence to reflect the intended expectations.	Suggestions: "Drug developers should use the assessment table as a tool for communication within and between drug developers and regulatory authorities across multidisciplinary teams to increase transparency and provide an understanding of MIDD at the planning stage and evidence submission stage. At the MIDD Planning stage, the assessment may be preliminary, recognizing that the model influence and context of use may change."
EFPIA	57	59	2	What is meant by subsections are organized into boxes?	
EFPIA	61	64		Improve structure of the text, separate definitions from step-wise process and purpose. Provide definitions first.	Suggestion: Position the table with definitions under line number 61, following "...are shown below:" - Move the statement: "The outcomes of the risk and impact assessments are denoted as "Model Risk" and "Model Impact"." underneath the table with definitions - Move the statement: "Model Risk is key for determining the requirements for Model Evaluation." under line number 81. - Move the statement: "Both Model Risk and Model Impact are used for MIDD planning, communication, and evidence assessment." under line number 83.
EFPIA	62		box	Consider including "model outputs" as well.	"A description of the model(s) and outputs(s) and their its specific role and scope to answer the question of interest."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Pharmetheus	64	65	2.1	The distinction between **model influence and model impact** is unclear, and the two terms appear to overlap. Additionally, how the two terms relates to MIDD planning, communication, and the outcome of the MIDD Evidence Assessment in a distinct manner is uncertain. To align with the ASMWE V&V40 risk-informed credibility assessment framework, we recommend removing the term "model impact" from the MIDD Evidence Assessment Framework. We believe "Model Risk" is sufficient to guide regulatory interactions and model evaluation.	
Pharmetheus	64	65	2.1	The term "Regulatory impact" has previously been used instead of "Model impact" and was categorized as Descriptive, Informing, or Replacing a clinical study, rather than being rated as Low, Medium, or High as suggested. Reverting to this established terminology may help differentiate it from "Model influence" (if the concept is retained, see comment above).	
Parexel	64	65	2.1	In the box, "Context of Use" is defined as "A description of the model(s) and its specific role and scope to answer the Question of Interest. The context should be outlined as a concise, clear, and explicit description of the model, [...]". It would be useful to clarify that this description, being required at the planning stage, does not correspond to the description of the final PopPK / exposure-response / PBPK model, with all compartments / parameters / features specified. We suggest to clarify that, in this case, "model description" is intended as the one usually provided in the data analysis plan, with the intent to show whether the proposed approach is appropriate to address the Question of Interest in a satisfactory manner.	
Parexel	64	65	2.1	In the box, for the definition of "Consequence of Wrong Decision", please clarify that "all available information" is intended as Model + other factors influencing the decision-making, to avoid ambiguity.	
Parexel	64	65	2.1	In the box, for "Model Risk" definition, please clarify the added value of this metric, as it incorporates elements derived from "Model Influence" and "Consequence of Wrong Decision".	
Parexel	64	65	2.1	In the box, based on definitions of "Model Influence" and "Model Impact", the two concepts appear to be strictly related. Could you please clarify whether the Model Influence is meant as the intended weight of the model, while the Model Impact is meant as the actual final weight of the model?	
EFPIA	64		Bullet 1	Add the definition information for question of interest from V V 40/FDA guidance	Suggestion: •Question of Interest: The question that MIDD is intended to answer (ie the specific question, decision, or concern that is being addressed)
EFPIA	64		Bullet 3	Add the definition information for model influence from V V 40/FDA guidance	Suggestion: • Model Influence: The intended weight of the model outcomes in decision-making considering the contribution of other relevant in-formation (ie the contribution of the computational model relative to other contributing evidence in addressing the question of interest (e.g., data from bench testing))
EFPIA	64		Bullet 4	The statement “based on all available information” does not provide any guidance and it is not instructive. What does all available information (to whom) mean?	Suggestion: “Consequence of Wrong Decision: The consequences (e.g., with respect to patient safety and/or efficacy) if a wrong decision is made, based on all available information.”

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	64		Bullet 5	Add the definition information model risk from V V 40/FDA guidance	Suggestion: •Model Risk: The contribution of the model outcomes to a pos-sible wrong decision and subsequent potential undesirable conse-quences (ie the possibility that the computational model and the simulation results may lead to an incorrect decision that would lead to an adverse outcome) Model Risk should be interpreted in the con-text of answering a specific Question of Interest and is not to be per-ceived as a risk intrinsic to MIDD or M&S. Model Risk assessment should be used for planning of, and alignment on, requirements for Model Evaluation and determination of the Outcome of the MIDD Evidence Assessment. The Model Evaluation should be commensu-rate with the Model Risk and be strengthened as it increases (see Sec-tion 3).
EFPIA	64		Bullet 5	The statement “and be strengthened as it increases”. is not informative. You can also add weakened as it decreases. Commensurate implies just that.	Suggestion: “The Model Evaluation should be commensurate with the Model Risk and be strengthened as it increases.”
EFPIA	64		Bullet 6	This is a new term not in VV40/FDA guidance but seems to align with the recommended scheme for assessing model risk that looks at combined impact = model influence + decision consequence. See FDA guidance page 18 Figure 2	Suggestion: •Model Impact: The contribution of the model outcomes in relation to current regulatory expectations or standards in answering the Question of Interest. Model impact assessment should include the influence of the model and the decision consequence. Model Im-pact assessment should be presented as part of communication and early alignment and will be used for determination of the Outcome of the MIDD Evidence Assessment.
EFPIA	64	65	2.1	Suggest that 64-65 list the definitions and the instructions discussed in subsequent text. "Context of Use" text is the same as lines 72-4.	Suggest text in 64-65 only list the definitions, and then discuss instructions in subsequent text.
EFPIA	64	83	2.1	The items listed in line 64 (boxed content) are repeated line 66-83 and the meaning of this separate listing remains unclear. The guidance will benefit from providing a clarification of this approach. It is proposed to only list the expectations once. If both listings are needed, an example (for planning & submission stage) is needed to understand the difference in their applicability.	
EFPIA	64	65	2.1	Section 2.1 (particularly the text in the box) would benefit from additional clarification. It is our understanding that 4 key assessment elements (rather than 6) are used to assess 1) Model Risk and 2) Model Impact. This section could be titled, "The evaluation of planned Model Risk and Model Impact" or similar, where it is descibed how the 4 key assessment elements (first 4 bulllets) are used in the overall model risk and impact evaluation. This also impacts the assessment table in Appendix 1.	
EFPIA	64	65	Section 2.1	The term "Wrong Decision" implies there are only 2 types of decisions (right vs. wrong), whereas the reality is more often a continuum.	BMS requests this term be changed to "Inappropriate Decision".
EFPIA	64	64	2.1	Model consequences in a preclinical setting may ultimately have impact on patient safety, but may be a few steps removed from an immediate direct consequece. Suggested revision broadens scope of application to acknowledge this	Replace 'patient safety' with 'safety'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	64	65	2.1	In bullet, the sentence: "Model Risk should be interpreted in the context..." is not clear.	Model Risk should be interpreted in the context of answering a specific Question of Interest and should not be perceived as an inherent risk of MIDD or M&S.
EFPIA	64	65	2.1	Bullets "Model influence and Model impact" should be merged into one bullet termed Model Impact because they are 2 sides of the same process, being the assessment model outcomes in relation to Question of Interest, regulatory standards and available information/data.	Merge bullets "Model influence and Model impact" into one bullet termed Model Impact with the instruction: The contribution of model outcomes in relation to answering the Question of Interest given current regulatory standards and available nonclinical and clinical data. Model Impact assessment should be presented as part of communication and early alignment and will be used for determination of the Outcome of the MIDD Evidence Assessment.
EFPIA	64	65	2.1	Model risk....is not to be perceived as a risk intrinsic to MIDD or M&S' is unclear. If this means about significant consequence of wrong prediction independent of modelling methods (e.g. DDI prediction for drugs with narrow therapeutic window), it should be rephrased	
EFPIA	64	65	2.1	Model impact....in relation to current regulatory expectations...' 1) suggest us to adapt the assessments for each region (e.g. pediatric PBPK <2yr is generally accepted by FDA but not necessary in the other regions) and 2) we need continuous communication (e.g., publications) from regulatory agencies about their view on maturity of modelling methods to address their regulatory decisions to standardize the assessment	
Parexel	65	85	2.1	Consider explicily mentioning that sensitivity tests may help estimate the levels of model risk	
EFPIA	65		box	It is confusing to understand how some of the terms are related or different and should be reorganized.	Suggestion: organizing terms slightly differently: Put "Model Influence" and "Consequence of Wrong Decision" under "Model Risk", to align with the texts from Line 75 to Line 81.
EFPIA	65		Table with Definitions	Improve structure of the text, separate definitions from step-wise process and purpose. Provide definitions first. Next sentences are not part of definition "Model Risk assessment should be used for planning of, and alignment on, requirements for Model Evaluation and determination of the Outcome of the MIDD Evidence Assessment. The Model Evaluation should be commensurate with the Model Risk and be strengthened as it increases (see Section 3)."	Suggestion: Move the statement: "Model Risk assessment should be used for planning of, and alignment on, requirements for Model Evaluation and determination of the Outcome of the MIDD Evidence Assessment. The Model Evaluation should be commensurate with the Model Risk and be strengthened as it increases (see Section 3)." to line number 81. Move the statement: "Model Impact: The contribution of the model outcomes in relation to current regulatory expectations or standards in answering the Question of Interest. Model Impact assessment should be presented as part of communication and early alignment and will be used for determination of the Outcome of the MIDD Evidence Assessment." to line number 83.
Parexel	66	85	2.1	For certain risk assessments such as model risk, model influence, potential consequences of wrong decision and regulatory impact a "traffic light" rating is required (low/green; medium/amber; high/red). These ratings could be less informative for various reasons and the focus should be on the justification provided by the applicant. Again examples could be given for increasing clarity, particularly for the regulatory impact item as the meaning of it may be unclear or can be misunderstood.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	66	85	2.1	The text following the Box in 2.1 seems redudant and confusing.	Suggest removing the text or provide additional necessary information that's not already stated in the Box.
EFPIA	66	85	2.1	Multiple models are often utilized to answer a question of interest. There should be some added clarity here on whether a formal model risk and model assessment should be performed for each of the models used and/or for the multiple models (assessed as a package) to answer the question of interest. Suggest adding a sentence related to multiple models risk & impact assessment in line 85	
Zhiyao Zhu/ PPD-Thermo Fisher	68	81	2.1	Although the 'Model Risk and Model Impact Assessment' is a multi-step process, it significantly overlaps with the 'Key Assessment Elements' highlighted in the black box earlier. This repetition makes the section somewhat redundant. Consider consolidating the content to enhance clarity and eliminate duplication.	
EFPIA	70	71	2.1	It should be noted that the QoI can be broader than the intended use of the model. This indicates that the model will be used to provide input to some aspects of a question, which is also clarified in the context of use. I assume that the opposite is also true; that a model can be developed with a broader intended use than the QoI -> to be used for several different QoI.	
EFPIA	71			The working definition in this document is context of use. “Context of Use” should be used consistently throughout the document.	Suggestion:“intended use” with “Context of Use”: “It should be noted that the Question of Interest can be broader than the intended context of use of the model.”
EFPIA	72	74		The current definition of "Context of Use" (COU) in the draft guidance is less than ideal. It includes a description of the model and data, which can detract from its primary purpose. The COU should instead focus on clearly defining the role and scope of the model in addressing the specific question of interest. By emphasizing the model's intended application and the decision-making context, the COU can better guide the model development, verification, and regulatory evaluation of the model. This approach ensures that the COU remains aligned with the overarching goals of MIDD. Examples of COU: The Context of Use (COU) is a critical concept in FDA regulatory guidances for drug development. It defines how a drug development tool (such as a biomarker or clinical outcome assessment) is intended to be used and its purpose in supporting the development of drugs or biologics. Here are some definitions from various FDA guidances: 1.Biomarker Qualification Program: The COU specifies how the biomarker is to be used and its purpose in drug development. This includes the specific drug development setting and the decisions the biomarker will inform. 2.Patient-Focused Drug Development: In the context of clinical outcome assessments, the COU describes the intended use of the assessment tool, including the specific disease or condition, the target population, and the type of clinical trial or study. 3.Drug Development Tools Guidance: The COU outlines the circumstances under which the tool is to be used, including the specific phase of drug development, and the decisions that will be informed by the tool.	Suggestion: reconsidering the definition of “Context of Use”.
EFPIA	72	74		Comment: Propose to add explicitly stating the assumptions and potential uncertainties behind the model structure and- if relevant- parameters Rationale: Explicit listing of assumptions and uncertainties at the planning stage can help in leading to a better choice of model(s) used in the MIDD approach	Suggestion: “Define the Context of Use: Provide a concise, clear, and explicit description of the model, the assumptions and uncertainties of the model structure and parameters, the data used to build the model, the specific role of the model outcomes, and the other data or evidence that will contribute to answering the Question of Interest.”

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	72	81	2.1	The definition of model risk is missing any assessment of confidence in the model, which should be an important component. The probability of the model being wrong should be accounted for as well as the influence and consequences of a wrong decision (that is, it seems the risk should be lower if you are very confident in the model, regardless of the consequences of a wrong decision, because the probability of making a wrong decision is lower). Confidence in the model could be added a component of Context of Use	Add confidence in the model as an element of the context of use and risk assessment, recognizing that this may change as model development progresses
EFPIA	75			Implementation challenges: There are concerns about the practical implementation of the guideline in terms of model risk assessment: Model influence and consequences of wrong decisions (and their associated ratings) are too subjective that may lead to lack of objectivity for model risk assessment.	Suggestion: providing a framework for model risk assessment: e.g. Framework for regulatory impact analyses for the PBPK model (EMA 2018 Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation).
EFPIA	75	81	2.1	In model risk assessment, a section identifying the limitations of the dataset in estimating certain parameters should also be explicitly stated as this can have a direct impact on uncertainties in dose projections. Model senstitivty analyses as explained in section 3 can then be directly aimed at mitigating this risk.	
EFPIA	75	77	2.1	Aligning Table 1 with the text in lines 75-77 is needed to show that Model Risk Assessment includes Model influence and consequence of wrong decision. The way it is currently shown in Table 1 gives the impression they're separate elements and not part of the Model Risk Assessment.	
EFPIA	75	85	2.1	It would be helpful to include examples to help clarify definitions of low, medium and high risk as provided in the FDA AI Risk-based credibility assessment framework	Include examples or reference to examples to clarify definitions of low/medium/high risk
EFPIA	75	81	2.1	Model risk maybe asessed differently amongst the industry and regulators	More guidance should be provided on model risk (using use case examples)
EFPIA	75	77	2.1	The weight of the model in (regulatory) decision making will often be challenging to know prospectively (depends on model quality/fit/results,…).	In lines 76-77: Use subjunctive form "the contribution of the model outcomes may have in the totality of evidence".
EFPIA	75	81	general	Rating model risk, influence, consequence and impact (Appendix 1) need some guidance or examples. It meant to be 'case-by case (p84)' but the rating has impact on the review efforts/scrutinity and therefore standardization of rating seems important	
EFPIA	80				Suggestions: “Combining both the impact of Model Influence and the Consequences of a Wrong Decision, the resulting Model Risk should be described and rated as low, medium, or 80 high, and then the rating justified.”
Song Wang/Thermo Fisher	82	83	2.1	More guidance is needed for evaluation of model impact. Maybe some examples would help people understand what types of impact is discussed here.	
EFPIA	82	83		Model Impact Assessment is not a term in V V 40 but seems to be similar to the Model Risk assessment/ratings in line 80-81. As this is a new term, clarification will be needed for this additional assessment and clarification on how this is different than Model Risk impact.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	82	83	Section 2.1	Clarification Requested: The terms "Model Impact" and "Regulatory Impact" are not clearly defined in the guidance. While "Regulatory Impact" is considered a component of "Model Impact," there is uncertainty regarding how to assess Regulatory Impact effectively and how it differs from Model Influence. Clarifying these definitions and distinctions would enhance understanding and facilitate more accurate assessments within the regulatory framework.	Requests additional text for clarification. It is recommended to include an example that illustrates how "Regulatory Impact" should be assessed by regulatory authorities or the sponsor. This example could provide clear guidance on the evaluation process, helping stakeholders understand the specific considerations and steps involved in assessing the impact of a model on regulatory decisions.
EFPIA	84	85	2.1	To avoid subjectivity in risk assessment, further guidance or examples would be appreciated	
EFPIA	86		Section 2.2	Section 2.2 “Additional Considerations for Interaction with Regulators and to Inform Decision-Making” contains content that is explained in the later sections, such as Model Evaluation. Therefore, audience might be confused when they read this section.	Recommendation moving section 2.2 “Additional Considerations for Interaction with Regulators and to Inform Decision-Making” to the end of the guideline.
EFPIA	88	98	2.2	Could wider recommendations on the technical criteria for model evaluation be provided	ICH can givea few more examplesacceptance criterias for specific model applications e.g. BE for PK predictions, Guest criteria for DDI evaluations etc.
Parexel	90	90	2.2	In the below box, for bullet point #2 (Technical Criteria): (i) the context behind the example for how to establish acceptability of the model (i.e. the example of bioequivalence acceptance limits) is not clear, please elaborate; this lack of clarity might come from the different interpretations of the word "applicability" (applicability as model validation, i.e. is the model good enough to answer the question, vs applicability intended as data interpretation, i.e. how to use model outcomes to answer the question of interest); (ii) Please add an example also for Model Evaluation (first part of the statement)	
Parexel	90	90	2.2	It is now specified only in footnote (#5) that items related to planning should be provided as well at the evidence submission stage. We suggest to re-iterate the message within the main text after the box for clarity.	
EFPIA	90		box	Technical Criteria: Using bioequivalence (BE) goalposts as a technical criteria for model evaluation is a poor choice of an example. BE criteria may be too stringent. Later in the guidance there are examples of numerical and visual predictive checks and these are more relevant to current modeling practices and much more suitable examples of model evaluation technical criteria.	Suggestion: “Technical Criteria: A summary and rationale of the key criteria for Model Evaluation and model outcomes to establish the acceptability of the model (e.g., using an acceptance standard such as bioequivalence acceptance limits).”
EFPIA	90	91	2.2	The bioequivalence critieria is not routinely used as model acceptance criteria, and may cause unnecessary confusion.	Suggest deleting this example criteria, or provide alternatives.
EFPIA	90	90	Section 2.2	Clarification requested to the table below Line 90: The guidance requests the establishment of acceptance standards for key criteria related to model evaluation and model outcomes. However, setting specific acceptance standards for model outcomes may not be appropriate.	For clarification, recommendation to remove the reference to "model outcomes" from the section on acceptance standards, as the outcomes of a model typically should not determine its acceptability. This adjustment will help clarify that the focus should be on evaluating the model's methodology and integrity rather than its results.
EFPIA	90	91	2.2	`Outcome of the MIDD Evidence Assessment: A concise summary of the multidisciplinary assessment of the MIDD evidence to answer the Question of Interest`.... Does this imply that a multidisciplinary MIDD aproach is used?	The language should be changed to provide more flexibility and be applicable to situations where only one M&S method is used.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	92	93		Consider the following rewording for “being strengthened”.	Recommedation to use the following rewording: "… with emphasis on the aspects of Model Evaluation activities (see Section 3) with increased rigor as Model Risk increase.
EFPIA	93	93	2.2	Clarification with regards to "strengthened" should be defined in Section 3 or here. Examples would be helpful in Appendices.	
EFPIA	93	93	2.2	...(see Section 3) being strengthened as Model Risk increases."	replace strengthened with "more rigorous".
EFPIA	97	98	2.2	M&S methods are expected to evolve across the development lifecycle as new data and results are generated. This may involve changes to the Technical Criteria. In this context, the guidance of "drug developers are encouraged to seek further alignment" does not provide sufficient specificity as to if and when this should occur.	Provide more clarity for the conditions that would warrant further alignment on changes to the Technical Criteria. Ideally, changes that are minimal and considered low risk (e.g., mathematical precision on a threshold value, use of an improved method for model validation, etc) should not require further, proactive alignment and can instead be incorpoated within a future submission document.
EFPIA	99	102	2.2	...drug developers should include model risk and impact assessment...the key results of the technical evaluation of the model. The drug developer should provide their initial conclusions on the Outcome of the MIDD Evidence Assessment." According to the table in Annex 1, model risk, impact an technical details are considered as part of evidence assessment.	Define clearly what MIDD Evidence Submission Stage requires
EFPIA	101	102		Consider emphasizing that the assessment is based on joint input from experts across different disciplines.	Suggestions: “The drug developer should provide their initial conclusions, which could be multidisciplinary in nature, on the Outcome of the MIDD Evidence Assessment.”
EFPIA	108	109	2.2	Early and multidisciplinary regulatory input seems to be restricted to EMA. At early stage also NSA or joint NSA may be considered if the expertise is in place.	
EFPIA	110	111	2.2	Please define what is meant that the Model Risk and/or Model Impact is expected to be high.	Define in what cases that a Model Risk and a Model Impact is high.
EFPIA	117	118	3	What are the 'current accepted standards and/or scientific practices with the specific M&S method(s)'?	Please provide proper guidance or reference.
EFPIA	124			Verification is not the appropriate technical term for the process being described in lines 124 to 127. The process is more synonymous with QC (quality control) procedures in modeling.	Recommedantion to change “verification” activities to “quality control” activities.
EFPIA	124	127		Add the definition information for verification from V V 40/FDA guidance	Suggestion: Verification is the process of determining that a computational model accurately represents the underlying mathematical model and its solution from the perspective of the intended uses of modeling and simulation. Verification activities aim to ensure user-generated codes (i.e., instructions written by the user of a programming language or software) for processing the data and conducting the analysis are error-free, equations reflecting the model assumptions and their representation in the programming language or software are correct, and calculations are accurate.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	124	127	3	The terminology of "verification" in this guideline seems to refer to QC and be different from the commonly accepted terminology in PBPK modeling, which has been defined in other regulatory guidance, eg, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-and-simulation_en.pdf and publications eg, https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12678	Suggest using more commonly accepted terminology and consistency across different guidelines. Also applicable to Appendices.
EFPIA	124	127	3	"User-generated" code should be clarified as to what this responsibility covers: sponsor generated code as well as external software packages, e.g. CRAN packages for R, packages from academia/industry collaboration, etc.	Suggest to change "user-generated" to sponsor generated.
EFPIA	125	127	3	Reproducibility is not mentioned throughout the document. While recognised it is not applicable to all modelling and simulation methodologies in scope, for some code provided should allow reproducibility of the simulation results presented. Therefore could consider adding as a verfication activity (noting only where applicable)	Add ensuring reproducibility as verfication activity (where applicable)
EFPIA	128			Currently, the definition of validation is very broad in the draft guideline which includes the data, the model's conceptual form (i.e., overall structure and complexity), the model assumptions, the approach to model development, and the graphical and numerical approaches to model performance and external validation.	Suggestion to split into two for more clarity – A. Model Development which should include the data, the model's conceptual form (i.e., overall structure and complexity), the model assumptions and the approach to model parameterization B. Model Validation – which should include graphical and numerical approaches to model performance and external validation.
EFPIA	128	133		Add the definition information for validation from V V 40/FDA guidance	Suggestion: •Validation is the process of determining the degree to which a model or a simulation is an accurate representation of the real world. Validation activities aim to assess the adequacy of the model robustness and performance. Validation activities include assessing the relevance and appropriateness of the following: the data, the model's conceptual form (i.e., overall structure and complexity), the model assumptions, the approach to model development, and the graphical and numerical approaches to model performance and external validation. An important underlying principle is the comparison of the model versus data, prior information, and knowledge.
EFPIA	128	128	3	Shall we rather talk about Qualification activities rather than Validation activities, as a model cannot be really validated?	
EFPIA	130	132		Model Validation is a very high bar. The approaches being described (except 'external validation') are more synonymous with Model Verification.	Suggestion: Validation activities include assessing the relevance and appropriateness of the following: the data, the model's conceptual form (i.e., overall structure and complexity), the model assumptions, the approach to model development, and the graphical and numerical approaches to model performance. Suggest moving the deleted text to the preceding paragraph under model verification activities.
EFPIA	133	133	3	"An important underlying principle is the comparison of the model versus data, prior information, and knowledge." What is meant by 'model versus data'?	Specify what data is need here (i.e., observed data, unseen data, etc.).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	134	137		Add the definition information for applicability from V V 40/FDA guidance	Suggestion: •Applicability of the model(s) (also referred to as “fit-for-purpose”) characterizes the relevance and the adequacy of the data and model’s contribution in answering a Question of Interest. Applicability should be assessed for each Question of Interest following assessment of validation and verification for the relevance of activities to support the use of the computational model for the context of use.
Parexel	136	137	3	As mentioned above (comment related to box after row #90), applicability might be interpreted differently, depending on whether the MIDD approach is at the planning (applicability as "appropriately designed for the intended purpose") or finalization phase (applicability as "final model actually fit for intended purpose"). Throughout the guidance, we suggest to better distinguish between planning phase and evidence submission phase in terms of definitions (such as the applicability one) and in terms of expectations.	
Song Wang/Thermo Fisher	140	141	3	What needs to be documented here? just each step of verification is done?	
Medicines for Europe	142	144	3	“The quality assurance of computer software used for M&S-related data management and analysis should be documented. This includes appropriate software testing procedures, including installation and version tracking. Refer to the ICH E6 Guideline for additional information on software validation.” a.From a QA perspective, the processes involving computerized systems can be validated at different levels (i.e. whole process validation, system validation, software validation, etc.). Given the wide different M&S models useful in MIDD and the variety of software and software combinations that can be used for their development, What level of validation is expected in the tools and process used for MIDD models? b.Would it be possible to consider different levels of validation such as a model development environment and a Model application environment?	
EFPIA	142	145		The quality assurance of computer software used for M&S-related data management and analysis should be documented	Request clarification of expectations for when commercial software is used.
EFPIA	142	145	3	Can the ICH comment and expand on the acceptability of the software and model evaluation provided by the software developers as a part of the partcular version release.	Proposed additional text "The appropriate software testing procedures procdures including installation, and version tracking. This reccomendation includes the use of default models and simulation approaches"
EFPIA	142	145	3	Some of the verification activities as described may be difficult for open source or commercially licensed software which access to underlying code and/or development activities may be restricted. If there are some benchmarks or minumum criteria which either code providers or code users can refer to to establish an acceptable standard for verification has been achieved that would be helpful.	Make clearer in text how acceptable verification may be achieved in scenarios where using open source or commercially licensed code
EFPIA	144	144	3	Reader is referered to ICH E6 for information on software validation. It is not clear on reading ICH E6 specifically what is applicable to modelling and simulation scenarios - can more specific reference be provided	Add detail of relevant sections of ICH E6 to consult
EFPIA	145	146	3	Qualification and Applicability instead of Validation and Applicability	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	148	150		Justification of excluding data is stressed here, but what about dealing with missing data and intercurrent events, especially clinical endpoints?	Suggestion: “In general, data selection, associated transformations, with special attention to missing data and imputations methods should be specified, justified, and documented in the MAP and Model Analysis Report (MAR).”
EFPIA	151	152	3	The model structure and parameters should be consistent with the available knowledge on drug characteristics...'	Consider adding rationale of model structure selection after multiple model structures and parameterizations have been explored.
EFPIA	154	155	3	Besides quantifying the impact of model misspecification and assumptions, should the likelihood of them being false be documented as well? Or is the intention to document only those that are highly likely? It's possible to have an assumption that is low likelihood of being false but of significant impact.	The following additional text bis proposed "M&S sssumptions should be explicitly identified, alternatives considered, and when relevant to model applicability, should be described and justified. Consideration with respect to the confidence in the assumption should be included in this justification"
EFPIA	154	155	3	I do not see the word "limitation" in the document. I think it should be added with "Applicability" which is "defined" as "fit for purpose" (line 134)	
EFPIA	159			The parameters define the model being assessed. In other words, changing the parameters also changes the model. It seems more logical to consider parameterization when assessing the robustness of a particular model. Otherwise, a class of models would be assessed.	Suggestion: “Model robustness should be assessed to characterize the dependency on data, parameters parameterization, assumptions…”
EFPIA	159			The terminology of robustness to parameters can be interpreted differently and therefore some more details on what is exactly meant with parameters could be useful.	suggests details on what is exactly meant with parameters be included.
EFPIA	159			What is meant by “robustness”? How can a model be robust or non-robust to data (outliers?), parameters (the actual values or which parameters are estimated/fixed?)	requests clarification on intent of “robustness” described.
EFPIA	159	166	3	Model evaluation ensures that models are reliable and applicable for decision-making. Predictive check, comparing model predictions with observed data, is a common model evaluation method which is not listed in this section.	Consider including Predictive Check in this section
EFPIA	160	160	3	Suggest adding another example	"…(e.g., sensivity analysis, or bootstrapping)."
Pharmetheus	167	168	3	"External validation with independent data is encouraged……" External evaluation can be performed (using a legacy model) when obtaining new data. However, for the updated final model, withholding data for a truly external evaluation of the complete model would mean that suboptimal information/data will have been used for model development. Therefore, we would advise against generally suggesting using a truly external evaluation of the final model to avoid inappropriate data splitting practices.	
EFPIA	169	169	3	What is the definition of 'fulfilled' Technical Criteria?	Be more specific of what a 'fulfulled' Technical Criteria would be.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	170			Simulation methods and scenarios should also account for missing data and intercurrent events. See also remark line 148-150	Suggestions: “Simulation method and scenarios should be described sufficiently to enable the evaluation of their plausibility and the relevance to model applicability and should account for parameter and assumption uncertainties, handling of missing data and intercurrent events.”
EFPIA	175			At the end of Line 175, consider adding concluding sentence/paragraph on using all the model evaluation activities to come to a final assessment on the model.	Suggestion: "After completing the model evaluation activities, an assessment should be conducted to determine if the model is deemed acceptable. This assessment considers the context of use, associated risks, verification and validation results. Based on the findings, the model may be deemed suitable for the intended purpose. Otherwise, modifications or refinements can be made to the model, context of use, or verification and validation activities."
Pharmetheus	180	187	4.1, 4.2	Avoid using abbreviations that conflict with those defined in other regulatory guidelines, such as '**MAR' - model analysis report**, which is well established as "missing at random." We recommend using the term "Analysis Report" without any abbreviation. Hence, we also recommend to align the naming of the **Model Analysis Plan (MAP)** with that used for the report and remove the word “model” from the term and only use analysis plan without any abbreviation.	Analysis Report Analysis Plan
EFPIA	180	186	4.1	Should the assessment table be included in the MAP?	
EFPIA	180	180		Term "Planning" is unusual	Model Analysis Plan
EFPIA	181	186	4.1	ICH recomends to pre-define model analysis plans. No specific recoomendatons on the use of model types has been recooemded for specific populations.	ICH are requested to at least recommend their preferences for use of model types in specific populations (e.g. PBPK for neonates, <2yr pediatrics).
EFPIA	186	186	4.1	Many M&S activities mentioned in the M&S method overview in the background section begin as exploratory efforts during drug development. As these activities progress through the development stages, their importance may increase, eventually becoming part of a regulatory interaction package. Consequently, MAPs for these activities might soon become outdated or irrelevant. Creating them once the MIDD activity gains regulatory significance would essentially duplicate the MAR, likely without any deviation. However, the impact, influence, and risk of the model can be evaluated in advance.	A one-page modeling outline considering the key assessment elements in the table in Appendix 1 should suffice for exploratory activities, being an option to eliminate the need for a full MAP.
EFPIA	187	192	4.2	It is unclear if the assessment table is recommended to included as part of the MAR, or is intended to be separate document	Please clarify
EFPIA	193	193	4.3	Provide clarity on whether including the table of assessment could be considered on a case by case basis, e.g. creating such assessment tables may not provide much value for low risk cases.	
Pharmetheus	195	196	4.3 & Appendix 1	We suggest adding a row to the Assessment of MIDD Evidence table titled **Integrated Summar**y, as it is specified that an integrated summary should be included within the assessment table when multiple sources of MIDD evidence are used.	Add row "Integrated Summary" to table

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	195	198	4.3	It is unclear if a table is expected for each individual model as well as the integrated assessment table	Please clarify
EFPIA	195	198	4.3	More clarity on content and format of assessment table for planning and submission need to be provided, particularly where there are many questions sharing the same model/ key assessment elements or slight differences that wouldn't warrant separate assessment tables	
EFPIA	195	198	4.3	It would be helpful to provide more details how to summarize MIDD evidence when multiple MARs address the same question of interest and the use of the assessment table in such cases.	
EFPIA	195	197	4.3	Not clear what should be done when MIDD evidence from a single MAR	
EFPIA	199	202	4.3	Clearer guidance and an example of the section where an assessment table is supposed to be located in the regulatory submission dossiers would be helpful (e.g. eCTD module 2.7.2 population PKPD analyses).	
Pharmetheus	203	203	4.3	The requirements for submitting data in the context of QSP models and simulations need clarification, as these models incorporate various types of data, including clinical, proprietary, and in-vitro data etc.	
EFPIA	203	206	4.3	Can more detail or reference to more detail on MIDD Evidence Submission Stage be provided to understand how this step will be achieved (this will help in preparation of materials for this stage) e.g. expected format for code to be provided in (i.e zipped folder with latest verion), single or multiple files for all supporting evidence etc	Addition of details of MIDD Evidence Submission Stage
EFPIA	209		Appendix 1 Model Risk	Add information for model risk from V V 40/FDA guidance	Suggestion: "The contribution of the model and simulation outcomes results may lead to a possible wrong decision and subsequent potential undesirable or adverse consequences."
EFPIA	209		Appendix 1 Model Impact	Model Impact definition needs more clarity. It appears the impetus for this metric has to do with the regulatory novelty and/or precedence of the proposed MIDD.	Proposal: instead of a low to high scale, a more apt scale based on that frame of mind (precedence) would make gradation more palatable.
EFPIA	209	210	Appendix 1	Many of the Items in Appendix 1 request a rating of low, medium or high in instructions and the criteria for assignments is unclear. The document will benefit by providing recommendations and suggested references to enable the user ratings.	Suggest providing guidance or recommendations for assigning low/medium/high rating.
EFPIA	209	210	Appendix 1	Sugestion to include example of a completed Table for Assesssment of MIDD evidence. Example does not need to be included in the guidance, but availble for use.	Suggest providing an example of a completed Table for Assessment of MIDD evidence
EFPIA	209	210	Appendix 1	It would be helpful to include 1 or 2 practical examples or case studies of MIDD applications (eg, dose selection, clinical trial design) to promote enhanced understanding and effective adoption by stakeholders	
EFPIA	209	209	Appendix1	The definition and rating of model risk are not clearly described and are highly correlated with model impact. The rating is likely to be medium or high, as a lower rating might not necessitate submitting a MIDD approach to address a specific question, especially if the question is primarily supported by other means. Additionally, if the model risk rating is high, the impact will also be high. Therefore, the distinction between these two concepts is unclear.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	211	212	Appendix 2	The appendix is very consistent with the typical format for a standard pharmacometric (e.g. population PK) MAR. Flexibility issues: The guideline may not allow enough flexibility for innovative modeling approaches (e.g. QSP, MBMA, assessment of bias for meta-analysis). Suggest a general statement to be provided in the preface to the appendix general statement in appendix.	Suggestion: "This appendix provides the key content typically found within a MAR, although the exact content may vary depending on the specific M&S methodology employed. This appendix can be adapted for the methodology that do not fit neatly into the prescribed template."
Parexel	216	216	Appendix 2	In the table, we would suggest to comment on deviations from MAP at the end of the Methods section, as a separate section between Methods and Results (such as Changes from Planned Analysis). In this way, methods different from MAP can be anticipated and justified before coming to Results, and can also be easily spotted by a Reviewer.	
EFPIA	216	216	Appendix 2 Table	Table states user generated code should be provided for the 'key models' - what is considered 'key' here - should all models be in scope or if not can 'key' be further clarified	Replace 'key models' with 'models'
EFPIA	217	271	Appendix 3	While the guideline includes a glossary, ensuring that all key terms are clearly defined and consistently used throughout the document is important. Additional definitions or clarification of terms like "model robustness" and "model performance" is needed.	
EFPIA	226	228		Sentence could be more nuanced. Considering all available information is not necessary.	Potential Impact of Incorrect Decisions: The potential impact (e.g. on patient safety and treatment efficacy) if a decision is made incorrectly.
Pharmetheus	255	258	Appendix 4	The term "Outcome of the MIDD Evidence Assessment" may be misleading and could be confused with regulatory assessment. Consider revising it for clarity.	Adequacy of MIDD evidence
EFPIA	134, 146	137, 169	3	It's unclear on the distinction of Validation and Applicability. Some of the wording for Applicability could also be part of the model validation. Is it necessary to have Applicability?	Suggest keeping it simple as Validation. Or provide more clear definition on Applicability and differentiate from Validation. Also applicable to Appendices.
EFPIA	180, 187			Suggest moving MAP & MAR to other section	Suggestion to make MAP part of section 'additional considerations to inform decision making' and MAR part of 'Model analysis reporting' section.
EFPIA	235, 248, 255			The terms MIDD evidence, model outcomes, and Outcome of the MIDD Evidence Assessment appear to be closely related. The current definitions seem to have quite significant overlaps.	Recommens the terms MIDD evidence, model outcomes, and Outcome of the MIDD Evidence Assessment be further defined to enhance clarity or be consolidated into a single term.
EFPIA	41, 47	48	Table 1	minor: "Planning and regulatory interaction" sequence is confusing since regulatory interaction also happens after the reporting.	Suggest just use "Planning" for the first sequene. Also adding a sequence of "Regulatory Interaction" after reporting - as mentioned in Section 2.2.
EFPIA	64,72	64	2.1	Context of use should discuss model assumptions and uncertainties with respect to Question of Interest and model impact.	For model risk and impact - add low, medium and high as scores

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	65, 82		box	Model Impact here seems to be specifically geared toward regulatory considerations, while all other items (QoI, CoU,Model Influence, Consequence of wrong decision and Model Risk) are relevant to drug development decision-making process. Suggest to clarify the different focuses.	Suggestion to use of "Regulatory Impact of MIDD" instead of "Model Impact" throughout to clarify the different focuses. Model Impact: Regulatory Impact of MIDD: •Conduct a Model Impact assessment: Assess Regulatory Impact of MIDD