INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG DEVELOPMENT

M15

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GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG DEVELOPMENT

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ICH Consensus Guideline

1. INTRODUCTION

1.1. Objective of the Guideline

This guideline provides general recommendations for planning, model evaluation, and documentation of evidence derived from Model-Informed Drug Development (MIDD), hereafter "MIDD evidence."[1] It establishes a harmonized assessment framework (including associated terminology) for MIDD evidence.

1.2. Background

For the purposes of this guideline, MIDD is defined as the strategic use of computational modeling and simulation (M&S)[2] methods that integrate nonclinical and clinical data, prior information, and knowledge (e.g., drug[3] and disease characteristics) to generate evidence.

The generated evidence is used to inform drug development and decision-making by drug developers, regulatory authorities, and other stakeholders.

M&S methods include but are not limited to the following.

- Population pharmacokinetics
- Physiologically based pharmacokinetics and biopharmaceutics
- Dose-exposure-response
- Model-based meta-analysis
- Quantitative systems pharmacology and toxicology
- Agent-based models

[1] MIDD evidence is defined as model outcomes that have been determined by application of the MIDD evidence assessment framework including Model Evaluation to be appropriate to inform the answer to the Question of Interest.

[2] While it is acknowledged that they are not always synonymous, the terms "model" or "modeling" are often used in this guideline to represent "M&S" to improve readability and reflect commonly used terminology.

[3] For the purpose of this guideline, the term "drug" is considered synonymous with investigational product, medicine, medicinal product, biological product, and pharmaceutical product; this includes "drugs" for which marketing authorization is sought.

- Disease progression models
- Artificial intelligence/machine learning

1.3. Scope of the Guideline

This ICH M15 Guideline on MIDD applies to both current and emerging M&S methods and applications. It focuses on assessment of MIDD evidence and provides recommendations for related regulatory interactions, reporting, and submission. 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, E11[R1]/E11A, E14, M12, E17, and E9/E9[R1]).

This guideline does not include details regarding technical aspects of model development. Model development should follow the general recommendations outlined in this guideline in conjunction with current accepted standards and/or scientific practices for the M&S method(s).

1.4. Outline of the Guideline

Drug development is a sequential and iterative process where MIDD can play an important strategic role. When MIDD evidence may contribute to the answer to Questions of Interest, early planning allows the data to be generated to be incorporated into the overall drug development plan. It is expected that new Questions of Interest may emerge, and the associated plan could evolve as data and knowledge accumulate. Some of these iterations may require engagement with regulatory authorities to gain alignment on the MIDD planning.

Accordingly, this guideline defines the framework for assessment of MIDD evidence to inform decision-making (Section 2) and its use across the sequence of “planning and regulatory interaction” through to “implementation, reporting, and submission.” This sequence is split into five distinct activities. The linkage between these activities and the relevant guideline sections and subsections is provided in the guideline overview (Table 1). It is recognized that some activities may not always be necessary, may be combined, or may happen concurrently. Similarly, the sequence of activities may not necessarily be in one direction, as newly arising data and insights may require some to be repeated.

47 **Table 1: Guideline Overview: Sequence of MIDD in Relation to the Relevant Guideline Sections**

Stages	**Planning and Regulatory Interaction**		**Implementation, Reporting, and Submission**		
Sequence of Activities	**Key Assessment Elements**	**Additional Considerations for Interaction with Regulator and to Inform Decision-Making**	**Model Evaluation**	**Model Analysis Reporting**	**Documentation for Regulatory Interactions and Submissions**
	• Question of Interest • Context of Use • Model Influence • Consequence of Wrong Decision • Model Risk • Model Impact	• Appropriateness of Proposed MIDD • Technical Criteria for model evaluation and model outcomes[1] These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation • Applicability assessment	• Model Analysis Report(s) (MAR)	• Regulatory documents, including + Outcome of MIDD Evidence Assessment + References to all relevant MAPs and MARs
Relevant Guideline Section	Section 2.1 and Appendix 1	Sections 2.2 and 4.1 and Appendix 1	Section 3	Section 4.2 and Appendix 2	Sections 2 and 4.3 and Appendix 1

Note: Terms used in this table are defined in relevant guideline sections.

[1] Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest.

Inform Decision-Making

48

2. FRAMEWORK FOR ASSESSMENT OF MIDD EVIDENCE

This section describes key concepts for assessing MIDD evidence to inform decision-making. To aid in regulatory interaction and submission, a table for assessment of MIDD evidence (hereafter "assessment table") is provided in Appendix 1.

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. Early alignment with regulatory authorities facilitates subsequent acceptance of MIDD evidence.

The following subsections are organized into boxes that provide definitions for the relevant assessment table elements, and then text providing instructions and guidance with respect to their use.

2.1. Key Assessment Elements

The key assessment elements and their definitions are shown below. The outcomes of the risk and impact assessments are denoted as "Model Risk" and "Model Impact." Model Risk is key for determining the requirements for Model Evaluation. Both Model Risk and Model Impact are used for MIDD planning, communication, and evidence assessment.

- Question of Interest: The question that MIDD is intended to answer.
- Context of Use: 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, the data used to build the model, the specific role of the model outcomes, and the other data or evidence that will contribute to the answer to the Question of Interest.
- Model Influence: The intended weight of the model outcomes in decision-making considering the contribution of other relevant information.
- 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.

- Model Risk: The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences. Model Risk should be interpreted in the context of answering a specific Question of Interest and is not to be perceived 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 commensurate with the Model Risk and be strengthened as it increases (see Section 3).

- 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.

The Model Risk and Model Impact assessment is a multiple-step process that is laid out as follows:

- Specify the Question of Interest: As a starting point, explicitly stating the Question of Interest that will be answered by MIDD provides a structure that helps inform multidisciplinary discussions. It should be noted that the Question of Interest can be broader than the intended use of the model.

- Define the Context of Use: Provide a concise, clear, and explicit description of the model, 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.

- Conduct a Model Risk assessment: The Model Risk is decided by combining (i) the contribution of the model outcomes in the totality of evidence for a given decision, i.e., Model Influence; and (ii) the potential Consequences of a Wrong Decision. Both Model Influence and Consequence of Wrong Decision should be described and rated as low, medium, or high, as defined by the Question of Interest and Context of Use, and then the rating justified. The resulting Model Risk should be described and rated as low, medium, or high, and then the rating justified.

- Conduct a Model Impact assessment: The level of regulatory impact should be described and rated as low, medium, or high, and then the rating justified.

The rating of low, medium, or high may vary on a case-by-case basis, making the justification of the rating of greatest importance.

2.2. Additional Considerations for Interaction with Regulators and to Inform Decision-Making

In addition to the key elements described in Section 2.1, the following should be included to inform decision-making related to MIDD planning and/or MIDD evidence submission and should be provided to regulators for relevant regulatory interactions.

MIDD Planning Stage:[4,5]

- Appropriateness of Proposed MIDD: The rationale for why the proposed MIDD is suitable to answer the Question of Interest and cover the related key assumptions and required data.
- 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).

MIDD Evidence Submission Stage:[4,6]

- Model Evaluation: A brief discussion of the key results and conclusions of the technical evaluation[7] of the model.
- Outcome of the MIDD Evidence Assessment: [8] A concise summary of the multidisciplinary assessment of the MIDD evidence to answer the Question of Interest.

[4] In general, MIDD planning and MIDD evidence submission occur sequentially. In practice, the same regulatory interaction may address topics related to MIDD planning and evidence submission.
[5] These items should also be provided at the MIDD Evidence Submission Stage.
[6] "Submission" in this context refers to relevant information provided to a regulatory authority throughout the lifecycle of a drug.
[7] Using the principles of Model Evaluation described in Section 3, with specific focus on Technical Criteria.
[8] "Assessment" in this context does not refer to any regulatory review activities or processes.

To facilitate regulatory interaction, drug developers should provide rationale for the Appropriateness of the Proposed MIDD with emphasis on the aspects of Model Evaluation (see Section 3) being strengthened as Model Risk increases.

The details of Technical Criteria should be documented (e.g., in a Model Analysis Plan [MAP] or meeting background materials; see Section 4.3), and drug developers are encouraged to share these with regulators for alignment; this is particularly important when Model Risk is high (see Section 4.1). If new information or data arise that result in changes to the Technical Criteria, drug developers are encouraged to seek further alignment (see Section 2.1).

For the MIDD Evidence Submission Stage, drug developers should include model risk and impact assessment outcome in addition to the summary of 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.

When regulatory input is sought at both MIDD Planning and Evidence Submission Stages, the drug developer is encouraged to directly request the review and input of a MIDD expert among other experts from the regulatory authority considering the Context of Use. The interactions and inputs received from other regulatory authorities on the same topic are encouraged to be summarized and shared.

As discussed in the introduction to Section 2, seeking early and multidisciplinary regulatory input is encouraged and facilitates subsequent acceptance of the proposed application, especially when M&S methods are novel or Model Risk and/or Model Impact is expected to be high.

3. MODEL EVALUATION

This section provides an overview of Model Evaluation elements (i.e., verification, validation, and applicability assessment) and related general recommendations. These elements should be used to determine the acceptability of the model(s) to answer the Question of Interest, forming the basis of MIDD evidence assessment to inform related decision-making (see Section 2). Model Evaluation should follow the current accepted standards and/or scientific practices associated with the specific M&S method(s) and be commensurate with Model Risk (see Section 2).

Descriptions of Model Evaluation and general recommendations in this section are intentionally presented at a high level to facilitate use across M&S methods. Adopting these recommendations ensures that appropriate actions have been taken to inform decision-making.

The elements of Model Evaluation are defined as follows:

- 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.

- 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.

- 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.

The following are general recommendations for the Model Evaluation elements:

Verification

- Verification of the key user-generated codes, equations, and calculations should be documented and available for review by regulatory authorities.

- 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.

Validation and Applicability

- The relevance and appropriateness of the data to answer the Question of Interest should be justified. The rationale for exclusion of data should be provided and the potential for bias assessed. In general, data selection, associated transformations, and imputations should be specified, justified, and documented in the MAP and Model Analysis Report (MAR).

- The model structure and parameters should be consistent with the available knowledge on drug characteristics, pharmacology, physiology, and disease pathophysiology, when relevant.

- Key M&S assumptions[9] should be explicitly identified, alternatives considered, and when relevant to model applicability, should be described and justified.

- M&S method-specific issues should be considered (e.g., selection bias for model -based meta-analysis, knowledge gaps for a mechanistic model, or overfitting for an artificial intelligence/machine learning model).

- Model robustness should be assessed to characterize the dependency on data, parameters, assumptions, and associated uncertainty (e.g., sensitivity analysis).

- Model performance (e.g., precision and bias) should meet general technical standards associated with the specific M&S method(s) and should be assessed using graphical and numerical metrics. The metrics that relate to the Question of Interest and associated analysis objective(s) (see Appendix 2) should be prioritized in Model Evaluation. As indicated in Section 2.2, drug developers are encouraged to gain alignment with regulatory authorities on Technical Criteria as part of the MIDD Planning Stage using the assessment table.

- External validation with independent data is encouraged in order to assess the adequacy of model performance and can increase confidence for its proposed application when associated Technical Criteria are fulfilled.

[9] Assumptions include but are not limited to data (e.g., imputation), model structure and parameters (e.g., derived or fixed based on prior information), and mathematical or statistical aspects of the model.

- 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.

- Predefined MAPs covering the Model Evaluation activities and Technical Criteria are recommended (see Section 4.1). Changes to the planned analyses should be justified, and these should be documented in the MAR.

4. MIDD REPORTING AND SUBMISSION

The following section provides recommendations on MAPs (Section 4.1), MARs (Section 4.2), and documentation (including the assessment table) with respect to regulatory interactions and submissions (Section 4.3).

4.1. Model Analysis Planning (MAP)

It is recommended to pre-define and document each model analysis in a MAP. Relevant elements of a MAP typically include the introduction, objectives (including intended model outcomes), data, and methods (e.g., details of technical criteria) that align with the corresponding MAR sections (Section 4.2 and Appendix 2). Provision of MAPs during regulatory interactions can facilitate discussions (see Section 2.2). This is particularly important when Model Risk is high.

4.2. Model Analysis Reporting (MAR)

The results of each model analysis submitted to regulators should be documented in a MAR. Descriptions of MAR sections are provided in Appendix 2. Key model outcomes described in a single MAR or multiple MARs that support the answer to a Question of Interest should be summarized using the respective assessment table (see Section 4.3 and Appendix 1). If a MAP was developed, it should be provided with the associated MAR.

4.3. Documentation for Regulatory Interactions and Submissions

The following are general recommendations for documentation of MIDD evidence:

- When MIDD evidence from multiple MARs and/or other sources supports a Question of Interest, an integrated summary should be provided in a concise manner within the

assessment table. Additional details should be provided in meeting background materials or Common Technical Document sections, with cross-references to source documentation.

- The assessment table and all relevant documents (e.g., MAPs, MARs, and clinical study reports) should be referenced or included in the most appropriate section(s) of the respective regulatory documentation (e.g., meeting background materials and Common Technical Document sections) in line with the Question of Interest.

- All stand-alone documents supporting submitted MIDD evidence, data used in M&S analyses, model coding scripts (e.g., the base and final models for population pharmacokinetics), and other relevant electronic files, definition files, and scripts used should be submitted or available for regulatory review and assessment.

- Inclusion of a summary of relevant regulatory feedback on MIDD is encouraged within background meeting materials and other relevant regulatory documents.

APPENDIX 1 TABLE FOR ASSESSMENT OF MIDD EVIDENCE

Item	Definition	Instruction	Entry
Key Assessment Elements			
Question of Interest[1]	The question that MIDD is intended to answer.	State the Question of Interest.	
Context of Use	A description of the model(s) and its specific role and scope to answer the Question of Interest.	Provide a concise, clear, and explicit description of the model, the data used to build the model, the specific role of the model outcomes, and the other data or evidence that will contribute to the answer to the Question of Interest.	
Model Influence	The intended weight of the model outcomes in decision-making considering the contribution of other relevant information.	Describe the Model Influence; rate it as low, medium, or high considering other relevant information (e.g., nonclinical and clinical) to inform decision-making; and justify the rating.	
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.	Describe the consequence of a wrong decision; rate it as low, medium, or high based on the severity of the consequences a wrong decision may have on patient safety and efficacy; and justify the rating.	
Model Risk[2]	The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	Describe the risk; rate it as low, medium, or high based on the Model Influence rate and the Consequence of a Wrong Decision rate; and justify the rating.	
Model Impact	The contribution of the model outcomes in relation to current regulatory expectations or standards in answering the Question of Interest.	Describe the impact; rate it as low, medium, or high considering current regulatory expectations or standards; and justify the rating.	
MIDD Planning Stage[3] The following items/rows are to be completed at the MIDD Planning Stage.			
Appropriateness of Proposed MIDD	The rationale for why the proposed MIDD is suitable to answer the Question of Interest and cover the related key assumptions and required data**.**	Include a description and justification sufficient to facilitate regulatory interaction on the appropriateness of the proposed MIDD to answer the Question of Interest.	
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).	Include a description of the Technical Criteria for the assessment of Model Evaluation and model outcome. This should include sufficient details on the relevant metric(s).	

Item	Definition	Instruction	Entry
MIDD Evidence Submission Stage The following items/rows are to be filled at the MIDD Evidence Submission Stage after data collection and execution of the model.			
Model Evaluation	A brief discussion of the key results and conclusions of the technical evaluation[4] of the model.	Describe the key results and how they compare to and fulfill the Technical Criteria and conclude on the acceptability of the model performance and model outcome, with details being provided in the appropriate regulatory documentation (see Section 4).	
Outcome of the MIDD Evidence Assessment[5]	A concise summary of the multidisciplinary assessment of the MIDD evidence to answer the Question of Interest.	Provide a multidisciplinary integrative assessment and conclusion for the acceptability of the MIDD evidence to contribute to the answer to the Question of Interest, referring to the MIDD assessment framework elements.	

[1] If MIDD is planned to answer different Questions of Interest, it is recommended to use separate tables for each question.
[2] Model Risk should be interpreted in the context of answering a specific Question of Interest and is not to be perceived as a risk intrinsic to MIDD or M&S.
[3] These items should also be provided at the MIDD Evidence Submission Stage.
[4] Using the principles of Model Evaluation described in Section 3, with specific focus on Technical Criteria.
[5] "Assessment" in this context does not refer to any regulatory review activities or processes.

APPENDIX 2 MODEL ANALYSIS REPORT CONTENT

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. As noted in Section 4.2, a single MAR or multiple MARs can provide model outcomes to answer Question(s) of Interest. The sections of the MAR, especially the objectives, may align directly with particular Question(s) of Interest or may have a broader perspective.

Sections	Content
Executive Summary	• An overview of the rationale for the analyses • A brief summary of the data and methods • A brief summary of the results and conclusions
Introduction	• The rationale for the analyses • Relevant background information and knowledge • If applicable, a description of pre-existing analyses with reference to previously submitted reports
Objectives	The objectives of the analyses

Data and Methods	Descriptions of the following:
	• Data sources
	  ○ Criteria and rationale with respect to source data inclusion and exclusion
	  ○ Relevant design features of studies and/or experiments
	• M&S methods, model development, and strategic approaches (e.g., the sequence of development, numerical methods, and Technical Criteria; see Section 2 and Section 3)
	• Approaches for Model Evaluation (i.e., verification, validation, and applicability; see Section 3)
	• If applicable, prediction and simulation methods and scenarios

Results	• Data description, including graphical and/or tabular displays, as appropriate. Data excluded during the analyses should be described along with appropriate rationale. • The results, including graphical and/or tabular displays, of model development and Model Evaluation, with predictions and simulations, if applicable • Any deviations from the MAP should be described and justified.
Discussion	Interpretation of results, including the adequacy, potential limitations of the data and M&S, and clinical and/or other implications, taking into account: • Deviations from the MAP • Model Evaluation (including Technical Criteria and applicability of the model) • Relevant nonclinical and clinical information and knowledge, if applicable
Conclusions	The conclusions of the analyses
References	A references list covering the sources of data used for the analyses (e.g., bioanalytical reports, clinical study reports, laboratory reports, or literature)
Appendices	Additional materials cross-referenced in the MAR, for example: • Supplemental data descriptions and model development and evaluation results, including graphical and/or tabular displays, as appropriate • The user-generated code for the key model(s)

APPENDIX 3 GLOSSARY

The following list of key terms and definitions is intended to promote consistent understanding and application of this guideline.

Applicability of the model(s):
Characterization of the relevance and the adequacy of the data and model's contribution in answering a Question of Interest.

Appropriateness of Proposed MIDD:
The rationale for why the proposed MIDD is suitable to answer the Question of Interest and cover the related key assumptions and required data.

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.

Context of Use:
A description of the model(s) and its specific role and scope to answer the Question of Interest.

MIDD evidence:
Model outcomes that have been determined by application of the MIDD evidence assessment framework, including Model Evaluation, to be appropriate to inform the answer to the Question of Interest.

Model Evaluation:
Model Evaluation refers to performing verification, validation, and applicability assessment of the model. For purposes of the assessment table, this should be presented as a brief discussion of the key results and conclusions of the technical evaluation of the model.

Model Impact:
The contribution of the model outcomes in relation to current regulatory expectations or standards in answering the Question of Interest.

Model Influence:
The intended weight of the model outcomes in decision-making considering the contribution of other relevant information.

Model-Informed Drug Development (MIDD):
The strategic use of computational M&S methods that integrate nonclinical and clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence.

Model outcomes:
Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest. These can be assessed as potential MIDD evidence using the associated framework.

Model Risk:
The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.

Outcome of the MIDD Evidence Assessment:
A concise summary of the multidisciplinary assessment of the MIDD evidence to answer the Question of Interest. “Assessment” in this context does not refer to any regulatory review activities or processes.

Question of Interest:
The question that MIDD is intended to answer.

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).

Validation:
A process that aims to assess the adequacy of the model robustness and performance.

Verification:
A process that aims 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.