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ICH M15: General Principles for Model-Informed Drug Development

Step 4 document

January 2026

Legal Notice

Background

- **This document has been signed off as a *Step 4* document (29 January 2026) to be implemented by the ICH Regulatory Members.**
- **This document was developed based on a Concept Paper (10 November 2022) and Business Plan (10 November 2022).**

Key Principles

- **For the purposes of this Guideline, Model-Informed Drug Development (MIDD) is defined as the use of computational modeling and simulation (M&S) methods that can include and integrate nonclinical data, clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence.**
- **This Guideline provides general recommendations for planning, model evaluation, and documentation of evidence derived from MIDD, hereafter "MIDD evidence."**
- **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.**
- **This Guideline establishes a harmonized assessment framework for MIDD evidence and provides an assessment table as a tool for communication between drug developers and regulatory authorities, across multidisciplinary teams, to increase transparency and provide an understanding of MIDD.**

Guideline Objectives and Scope

Objectives

- **To provide general recommendations for planning, model evaluation, and documentation of MIDD evidence**
- **To establish a harmonised assessment framework (including associated terminology) for MIDD evidence**
- **To facilitate a multidisciplinary understanding of MIDD and associated evidence generation**

Guideline Objectives and Scope

Scope

- **Applies to both current and emerging M&S methods, approaches, and applications**
- **Focuses on assessment of MIDD evidence and provides recommendations for related regulatory interactions, reporting, and submission**
- **Does not focus on details regarding technical aspects of the model development process. Model development should be consistent with the general recommendations outlined in this Guideline.**

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Background

- **M&S methods and approaches include, but are not limited to, the following:**
  - Population pharmacokinetics and pharmacodynamics
  - Physiologically based pharmacokinetics and biopharmaceutics
  - Exposure-response
  - Model-based meta-analysis
  - Quantitative systems pharmacology and toxicology
  - Agent-based models
  - Disease progression models
  - Artificial intelligence/machine learning

Outline of the Guideline

Guideline Overview in Relation to MIDD Planning and MIDD Evidence Submission

MIDD Planning[1] and Regulatory Interaction		**Implementation, Reporting, and MIDD Evidence Submission[2]**		
Key Assessment Elements	**Additional Considerations for Interaction with Regulators 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	• Technical Criteria for Evaluating Model and Model Outcome[3] • Appropriateness of Proposed MIDD These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation and Applicability Assessment	• Model Analysis Report(s) (MAR)	• Regulatory Documents, Including Complete Assessment Table: + Evaluation of Model(s) and Model Outcomes + Outcome of MIDD Evidence Assessment + References to All Relevant MAPs and MARs
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

Inform Decision-making

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

[1] MIDD planning refers to any timepoint when drug developers are planning MIDD activities, generally prior to availability of model outcomes relevant to the current question of interest. Planning may include internal activities; however, for the purpose of this Guideline, the focus is on consultation between drug developers and regulatory authorities.

[2] MIDD evidence submission refers to any timepoint when model outcomes are considered as MIDD evidence and submitted to regulators. This generally refers to submission for marketing applications and also includes other regulatory interactions.

[3] Model outcomes are 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.

Framework for Assessment of MIDD Evidence

- **Describes key concepts for assessing MIDD evidence to inform decision-making, increase transparency, and provide an understanding of the proposed MIDD strategy, its implementation, and available results with respect to provision of MIDD evidence**
- **These concepts are split into:**
  - Key Assessment Elements
  - Additional Considerations for Interaction with Regulators and to Inform Decision-making

Key Assessment Elements

- **Question of Interest:** The question that MIDD is intended to answer
- **Context of Use:** The role and scope of the model(s) used to answer the question of interest
- **Model Influence:** The intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence
- **Consequence of Wrong Decision:** The potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information
- **Model Risk:** The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences
- **Model Impact:** The extent to which the proposed MIDD strategy varies from regulatory standards, or expectations when no regulatory standard is in place, for answering the question of interest

See Guideline for additional details, including how to derive these elements. For ease of use, see separate Word version of Table for Assessment of MIDD Evidence.

Additional Considerations for Interaction with Regulators and to Inform Decision-making

- **Technical Criteria:** Key criteria for evaluating the model and model outcomes, and that are needed to inform MIDD evidence acceptance, contributing to the answer to the question of interest
- **Appropriateness of Proposed MIDD:** The rationale for why the proposed MIDD is suitable to answer the question of interest
- **Evaluation of Model(s) and Model Outcomes:** A brief discussion of the key results and conclusions of the technical evaluation of the model and model outcomes
- **Outcome of the MIDD Evidence Assessment:** The multidisciplinary team's assessment and conclusion on whether the model outcomes are considered MIDD evidence

See Guideline for additional details, including guidance with respect to regulatory interactions and submissions. For ease of use, see separate Word version of Table for Assessment of MIDD Evidence.

Table for Assessment of MIDD Evidence

Item	Definition	Instruction	Entry
Key Assessment Elements Key assessment elements are expected to be included in the assessment table regardless of whether it is used at planning or submission stages.			
Question of Interest[1]	The question that MIDD is intended to answer.	Explicitly state the question of interest. This should reflect and inform multidisciplinary assessments and regulatory decision-making.	
Context of Use	The role and scope of the model(s) used to answer the question of interest.	Provide a concise, clear, and explicit description of the model, its role and scope, and the data used to build the model. In addition, discuss any additional data or evidence that will inform the answer to the question of interest.	
Model Influence	The intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence.	Describe the model influence; rate it as low, medium, or high; and provide a justification for the rating.	
Consequence of Wrong Decision	The potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information.	Describe the consequence of a wrong decision; rate it as low, medium, or high; and provide a justification for the rating.	
Model Risk[2]	The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	The model risk is derived by combining model influence and consequence of wrong decision. Describe the model risk; rate it as low, medium, or high; and provide a justification for the rating.	
Model Impact	The extent to which the proposed MIDD strategy varies from regulatory standards, or expectations when no regulatory standard is in place, for answering the question of interest.	Describe the model impact; rate it as low, medium, or high; and provide a justification for the rating.	

Note: This table should be used to provide concise information. Details should be provided in appropriate supportive documents (e.g., in a MAP or regulatory interaction background materials).

[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.

Table for Assessment of MIDD Evidence

Item	Definition	Instruction	Entry
Additional Considerations for Interaction with Regulators and to Inform Decision-making MIDD Planning Stage[3] The following items/rows are to be completed at the MIDD planning stage:			
Technical Criteria	Key criteria for evaluating the model and model outcomes, and that are needed to inform MIDD evidence acceptance, contributing to the answer to the question of interest.	Provide a clear and concise description of, and rationale for, the technical criteria, which are specific to the question of interest.	
Appropriateness of Proposed MIDD	The rationale for why the proposed MIDD is suitable to answer the question of interest.	Provide a brief discussion of why and how the proposed MIDD is considered appropriate for answering the question of interest, taking into account aspects of the key assessment elements and including information on how the technical criteria are suitable to ensure the appropriateness.	
MIDD Evidence Submission Stage The following items/rows are to be filled at the MIDD evidence submission stage:			
Evaluation of Model(s) and Model Outcomes	A brief discussion of the key results and conclusions of the technical evaluation[4] of the model and model outcomes.	Provide a concise summary of the technical evaluation of the model and model outcomes and describe how they fulfill the technical criteria.	
Outcome of the MIDD Evidence Assessment[5]	The multidisciplinary team's assessment and conclusion on whether the model outcomes are considered MIDD evidence.	Provide a concise multidisciplinary assessment and conclusion of whether the model outcomes are considered MIDD evidence. This should integrate all of the assessment elements. Also provide a concise summary of the MIDD evidence related to the question of interest.	

Note: This table should be used to provide concise information. Details should be provided in appropriate supportive documents (e.g., in a MAP or regulatory interaction background materials).

[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.

Model Evaluation

- **Provides an overview of model evaluation elements and related general recommendations for determination of the acceptability of the model(s) to answer the question of interest**
- **Adopting these recommendations ensures that appropriate actions have been taken to inform decision-making.**
- **Model evaluation should at minimum meet the current accepted standards, if available, and/or established scientific practices associated with the specific M&S method(s) and be commensurate with model risk.**

See Guideline for additional details for the general model evaluation recommendations.

Model Evaluation

- **Elements**
  - **Verification**: Ensuring user-generated codes are error-free, equations reflecting the model assumptions and their representation in the programming language or software are correct, and calculations are accurate
  - **Validation and Applicability Assessment**: Assessing the model performance and robustness, including assessing the adequacy and relevance of the following: the data, the model's conceptual form (e.g., overall structure and complexity), the model assumptions, the approach to model development, the graphical and numerical diagnostics, and the external validation. Validation focuses on the overall comparison of the model versus data, prior information, and knowledge, while applicability assessment focuses on the adequacy of the data and model for each intended use.

MIDD Reporting and Submission

- **Provides recommendations on MAPs, MARs, and documentation for regulatory interactions and submissions (including the assessment table)**
- **Model Analysis Plan (MAP)**
  - Pre-define[1] and document each intended model analysis
  - For regulatory interactions, providing a MAP that defines the M&S can facilitate discussions.
- **Model Analysis Report (MAR)**
  - Document results of each model analysis submitted to regulators
  - M&S results should be described, and interpretation of results and model evaluation should be discussed.

See Guideline for additional details and an appendix outlining MAR content.

[1] For the purposes of this guideline, “pre-define” refers to documentation prior to accessing the data or performing the analysis, as appropriate considering the context of use.

MIDD Reporting and Submission

- **Documentation for Regulatory Interactions and Submissions**
  - The assessment table should be used as a communication tool throughout interactions with regulatory authorities during the MIDD planning stage and MIDD evidence submission stage.
  - The assessment table should be included in the most appropriate section(s) of the respective regulatory documentation (e.g., regulatory interaction background materials and Common Technical Document sections) in line with the question of interest.
  - Additional relevant documents, such as individual MAPs or MARs, should be cross-referenced within the assessment table and other relevant regulatory documents.
  - Additional details not included in those documents, such as further descriptions of the integration of multiple models or multiple sources of evidence to answer the question of interest, should be described in other relevant regulatory documents.
  - Inclusion of a summary of previously received regulatory feedback on the MIDD is encouraged to be provided within relevant regulatory documents.

Results of Public Consultation

- **Public comments resulted in changes to the Guideline, including clarifications of the assessment table elements and expectations regarding regulatory interactions.**
- **Public comments also indicated the value of examples using the assessment table. These will be generated as part of the training materials for this Guideline.**

Considerations

- **This Guideline should be used in conjunction with relevant topic-specific ICH Guidelines (e.g., E4, E5(R1), E6(R3), E7, E9(R1), E11(R1), E14, E17, M12, M13(A-C), and S7B).**
- **Additional training materials will be developed to complement this Guideline.**

Guidelines for Implementation

- **Use of the terminology in this Guideline will facilitate communication between drug developers and regulatory authorities.**
- **Detailed implementation of the Guideline, including placement of the assessment table(s) in regulatory documentation, will vary based on the question of interest.**

Conclusions

- **The guidance on assessment of MIDD evidence, model evaluation, and MIDD reporting and submission provided in this Guideline is intended to facilitate the use of MIDD evidence to inform decision-making.**
- **Early planning and inclusion of MIDD into the overall drug development plan ensures that the necessary data are generated to support MIDD strategies.**
- **Effective communication and early alignment with regulatory authorities regarding planned MIDD strategies facilitates the subsequent acceptance of MIDD evidence.**
- **The assessment table provides a tool for communication between drug developers and regulatory authorities, across multidisciplinary teams, to increase transparency and enable early alignment to facilitate subsequent acceptance of MIDD evidence.**

Contact

- **For any questions, please contact the ICH Secretariat:**

admin@ich.org