

# Harmonization of Mechanistic Model Performance Evaluation: An Industry Perspective

ACCP 2026 Annual Conference

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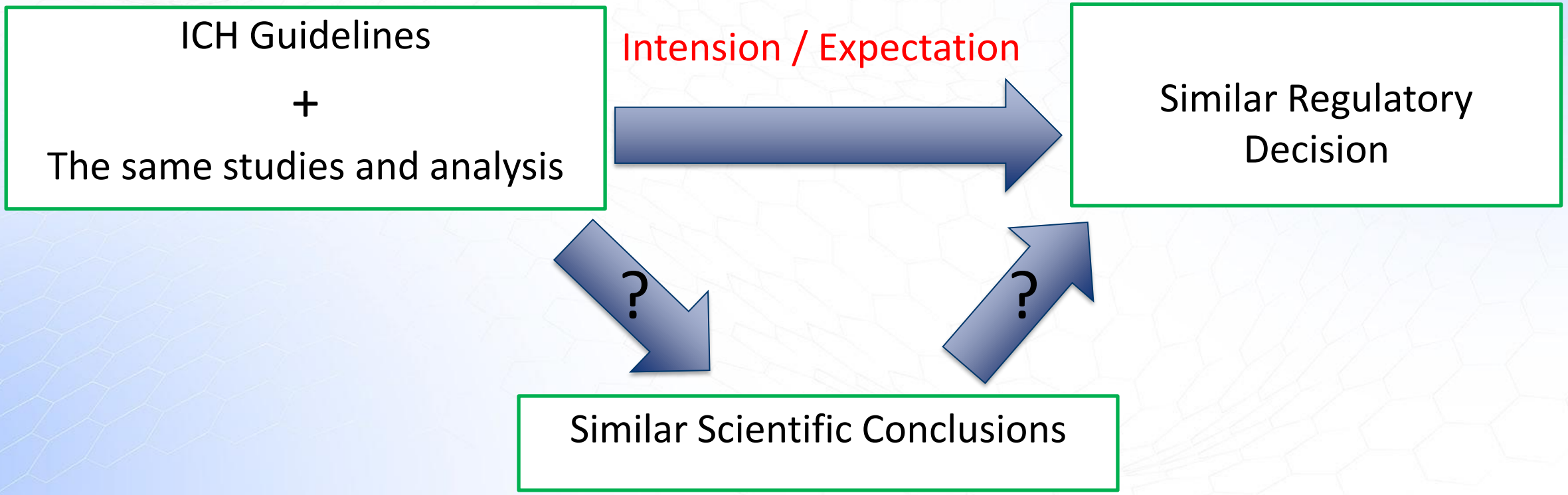
# Disclaimers

- The views expressed in this presentation are those of the speaker and do not necessarily reflect those of her employer.
- The comparison and interpretation of the EMA and FDA assessments are based on publicly available assessment and review documents.
- It is assumed that the same data package was submitted to both the EMA and FDA for the same type of applications of the same drug.
- The intention of this comparison is not to question or challenge the decisions of either agency, but to promote greater regulatory harmonization.


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# Global Harmonization Expectations

ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards.




ICH Official web site : ICH

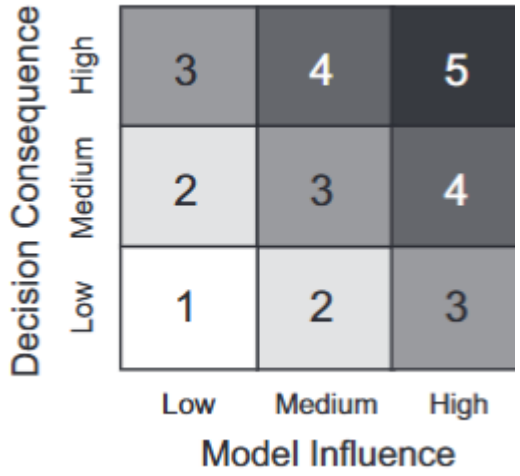

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# ICH M15 MIDD Guidance: Risk-Based Credibility Assessment

Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation

FDA Guidance for Industry and Other Interested Parties (2025): Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products

ICH M15 General Principles for Model-Informed Drug Development



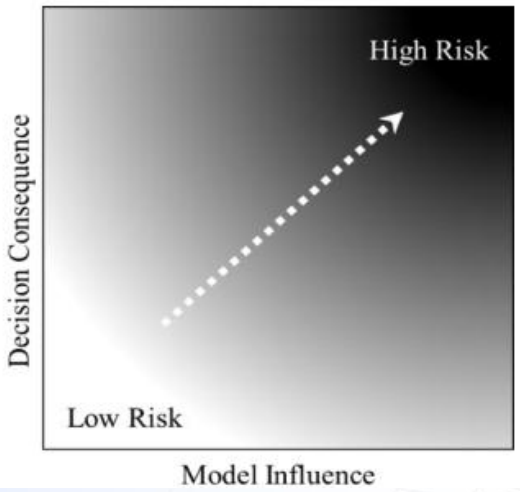




**Table 1: Guideline Overview: Sequence of MIDD in Relation to the Relevant Guideline Sections**

| 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<br>• Context of Use<br>• Model Influence<br>• Consequence of Wrong Decision<br>• Model Risk<br>• Model Impact | • Appropriateness of Proposed MIDD<br>• Technical Criteria for model evaluation and model outcomes[1]<br><br>These should be documented (e.g., in a Model Analysis Plan [MAP]). | • Verification<br>• Validation<br>• Applicability assessment | • Model Analysis Report(s) (MAR) | • Regulatory documents, including<br>+ Outcome of MIDD Evidence Assessment<br>+ 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**

"the performance acceptance criteria should be more stringent and described to FDA in more detail for high-risk models compared to low-risk models."


- Kuemmel C, et al. (2020) PMID: 31652029; DOI: 10.1002/psp4.12479
- FDA Guidance for Industry and Other Interested Parties (2025): Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products
- ICH M15 General Principles for Model-Informed Drug Development



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# Table for Assessment of MIDD Evidence

| Item | Definition | Instruction | Entry |
|---|---|---|---|
| **Key Assessment Elements**<br>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. | |

| Item | Definition | Instruction | Entry |
|---|---|---|---|
| **Additional Considerations for Interaction with Regulators and to Inform Decision-making**<br>MIDD Planning Stage[3]<br>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<br>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.<br>Also provide a concise summary of the MIDD evidence related to the question of interest. | |

ICH_M15_EWG_Workplan_2026_0217
ICH Official web site : ICH


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# PBPK Analyses for DDI Evaluation by Regional and ICH Guidelines

| Region | FDA (US) | EMA (EU) | PMDA (JP) | ICH M12 |
|---|---|---|---|---|
| **Relevant guidelines** | In Vitro DDI (2017), Clinical DDI (2017), PBPK Format (2018) | DDI Guideline (2012), PBPK Reporting (2018) | DDI Guideline (2019), PBPK Report Guide (2020) | ICH M12 (2022/2024 Final) |
| **CYP enzyme mediated DDIs** | Yes | Yes | Yes | Yes |
| **Transporter mediated DDIs** | Yes | Yes | Yes | Yes |
| **Predict the magnitude of DDI in specific population (s)** | Yes, such as in patients with renal impairment or patients with genetic deficiencies in certain metabolizing enzymes. | Yes, such as DDI in genetic subgroups and in pediatrics | Yes, can be used to evaluate DDI in special population or populations with specific diseases | Not mentioned |
| **Inclusion of metabolite-mediated DDIs** | Yes | Yes | Yes | Yes |
| **Requirement for model validation / verification** | Yes | Yes | Yes | Yes |
| **Sensitivity / Uncertainty analysis** | Yes | Yes | Yes | Yes |
| **Platform qualification** | Not required | Yes | Refer to model qualification (validation + sensitivity analysis) | Not required |

Modified from Zhang X. et al. Application of PBPK Modeling to Support Clinical Pharmacology Regulatory Decision-Making in The Art and Science of Physiologically-Based Pharmacokinetics Modeling (2024) 1st Edition CRC Press


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# Method

Survey CDER novel drug approvals (Jan 2025 – June 2026)

N = 70

Published reviews that include PBPK submissions

N = 30

Cross check against EMA database, identify Marketing Authorisation Applications that include PBPK submissions

N = 10

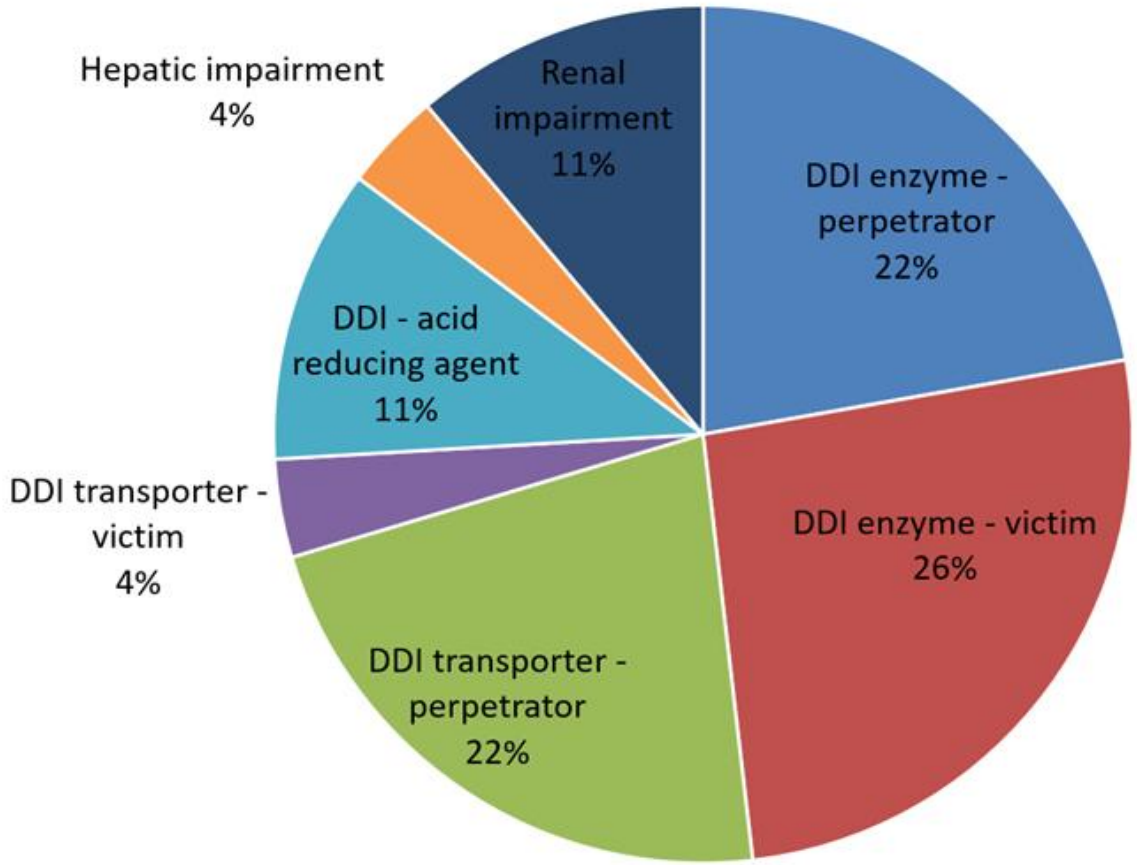
Among the 30 submissions to FDA, ICH M15 risk assessment was included in two PBPK reviews.

Novel Drug Approvals for 2025 | FDA
European Medicines Agency (EMA)
Drugs@FDA: FDA-Approved Drugs

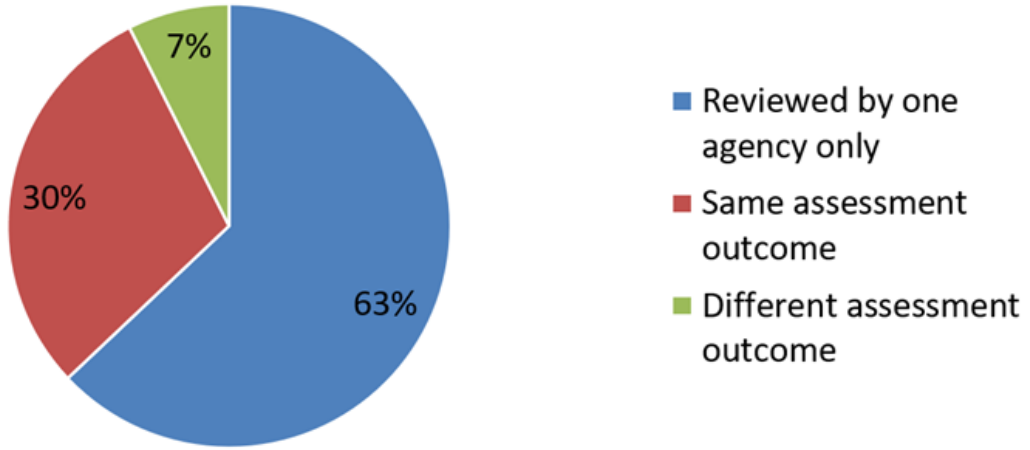

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# Statistics of the Survey Dataset

**Total # intended uses = 27**
**Total # of drugs = 10**




**Total # of intended uses = 27**
**Total # of drugs = 10**




| Outcome | EMA (%) | FDA (%) |
|---|---|---|
| Qualified / adequate | 22 | 44 |
| Insufficient / inadequate | 26 | 26 |
| Not reviewed | 52 | 26 |
| Partially adequate | 0 | 4 |

- When there is no assessment conclusions, it is included in “not reviewed”.
- When the conclusion is “supportive”, it is included in “qualified / adequate”.
- Partially adequate is due to multiple pathways in one category.


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# Comparison of Assessment Outcomes for Each Intended Use

| Intended Uses | Count | Qualified / adequate | | Insufficient / inadequate | | Not reviewed | | Partially adequate | |
|---|---|---|---|---|---|---|---|---|---|
| | | FDA | EMA | FDA | EMA | FDA | EMA | FDA | EMA |
| DDI enzyme - perpetrator | 6 | 4 | 1 | 1 | 1 | 1 | 4 | 0 | 0 |
| DDI enzyme - victim | 7 | 6 | 3 | 0 | 0 | 1 | 4 | 0 | 0 |
| DDI transporter - perpetrator | 6 | 0 | 0 | 4 | 4 | 1 | 2 | 1 | 0 |
| DDI transporter - victim | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| DDI - acid reducing agent | 3 | 1 | 0 | 1 | 0 | 2 | 2 | 0 | 0 |
| Hepatic impairment | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Renal impairment | 3 | 0 | 2 | 1 | 0 | 2 | 1 | 0 | 0 |

- In some FDA reviews, the original model was deemed inadequate, and FDA reviewers conducted additional simulations to address the shortcomings.
- In some reviews involving multiple pathways, the assessment outcomes could be partially inconsistent.


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# Reasons for PBPK Model Inadequacy

- Insufficient model validation / verification
- Poor predictive performance / model performance limitations
- Unjustified assumptions or parameters
- Model structure concerns or missing mechanisms
- Inadequate qualification dataset
- Lack of in vitro-in vivo extrapolation


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# Gaps and Solutions to Support Harmonization in Regulatory Assessments of PBPK Modeling

The majority of the applications included in the survey were submitted prior to the implementation of ICH M15 guidance.

| Gaps | Solutions |
|---|---|
| • Variability in assessment approaches, criteria, and expectations among reviewers within the same regulatory agency. | • Education and training sessions<br>• Establish communication channels across different agencies within and outside of specific programs;<br>• Consider similar program as the 'Project Orbis' for specific programs under review. |
| • Different regulatory expectations, modeling standards, or acceptance criteria across agencies | |
| • Different review process:<br>  • FDA reviewers run the models and may conduct additional simulations to address the shortcomings. | |
| • Limited opportunities for real-time discussion or knowledge exchange across regulators assessing similar models or products. | |


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# Summary

- Surveyed recently published PBPK applications (January 2025–June 2026) in EMA and FDA assessments
- 10 applications / 27 intended uses
  - 63% were reviewed by only one Agency
  - 30% received the same assessment from both Agencies
  - 7% received different assessment outcomes from the two Agencies
- Key drivers of model inadequacy:
  - Insufficient validation, Poor predictive performance, Unjustified assumptions/parameters, Structural/mechanistic concerns


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