EMA
EUROPEAN MEDICINES AGENCY

Guideline on assessment and reporting of mechanistic models used in the context of model informed drug development

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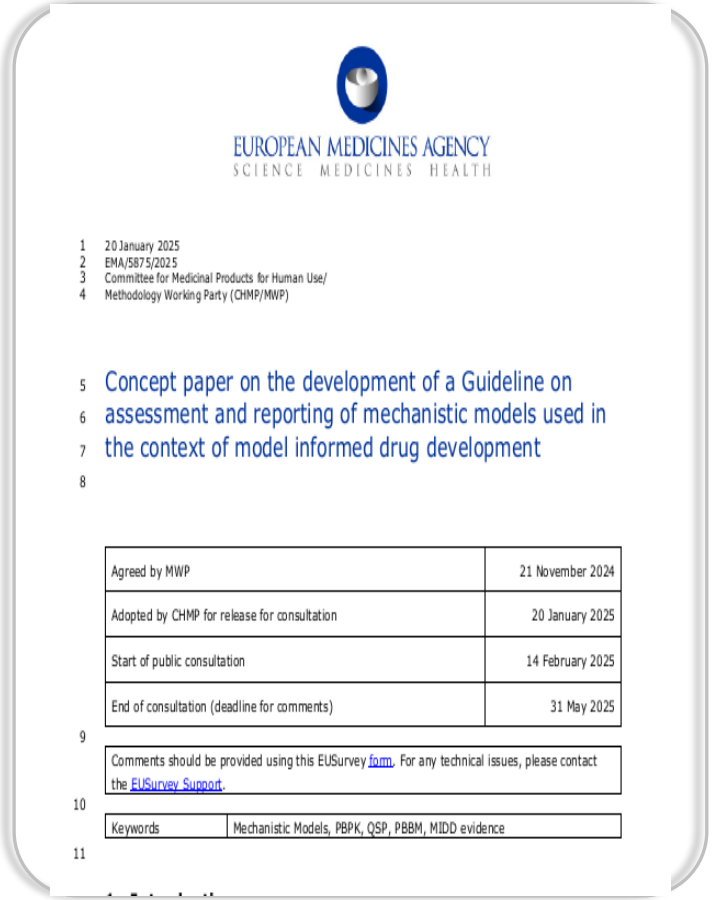
- Concept paper
- Overview of comments received
- Next steps toward the guideline

Concept paper

Objectives

- Streamline terminology and definitions related to mechanistic models.
- Model verification, validation and applicability assessment in alignment with ICH M15 GL including:
  - Regulatory expectations around the theoretical justifications of model structure and handling of uncertainty in supporting data sources.
  - Requirements to account for model uncertainty.
- Reporting of mechanistic models including requirements for code, structure, and source data.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 20 January 2025
2 EMA/5875/2025
3 Committee for Medicinal Products for Human Use/
4 Methodology Working Party (CHMP/MWP)

5 Concept paper on the development of a Guideline on
6 assessment and reporting of mechanistic models used in
7 the context of model informed drug development
8

Agreed by MWP	21 November 2024
Adopted by CHMP for release for consultation	20 January 2025
Start of public consultation	14 February 2025
End of consultation (deadline for comments)	31 May 2025

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Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

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Keywords	Mechanistic Models, PBPK, QSP, PBBM, MIDD evidence

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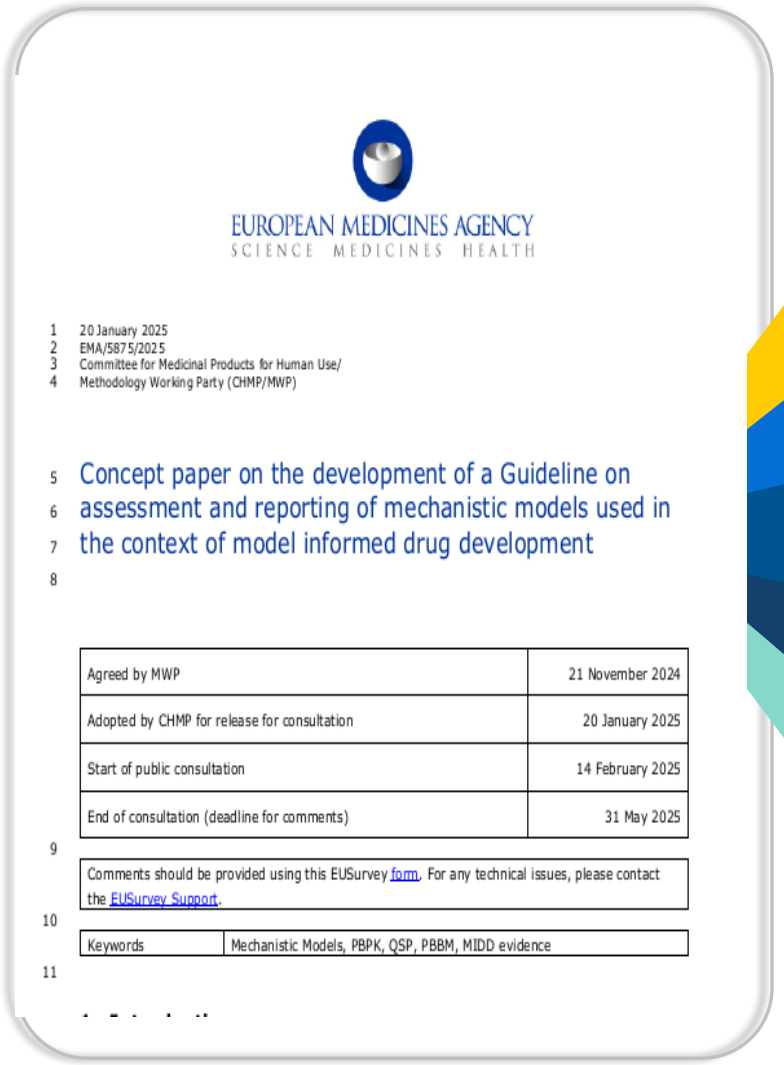
Concept paper



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Streamline terminology and definitions related to mechanistic models.

Model verification, validation and applicability assessment in alignment with ICH M15 GL

- Regulatory expectations around the theoretical justifications of model structure and handling of uncertainty in supporting data sources.
- Requirements to account for model uncertainty.

Reporting of mechanistic models including requirements for code, structure, and source data.

Public comments received

Public comments received (selected)

'It is great that this concept paper will explicitly address **aspects not covered in existing guidelines**. It would be beneficial to define and differentiate requirements (e.g., validation, reporting) based on context of use (CoU), model impact, decision risks, and development phases). '

*'The only aspect of QSP model development that is important but not mentioned is **the model development process**, which includes building up the model through creation of smaller or preclinical models, calibration of these models to data, and use of calibrated parameters in the larger model. Guidance should be given on **best practices for the utility of these smaller models** in minimizing uncertainty in parameter values, and in what case/what **types of parameters** they are appropriate for use.'*

Exploration of systematic use of study data to support regulatory assessment and decision-making

Scope & Definitions

Clear Scope Needed: Precise definitions of “mechanistic models”; clarification on AI/ML models, high throughput PBPK/ML models being in/out of scope; general GL vs. separate GLs for different type of mechanistic models
Consistency and harmonization of terminology: Calls for consistent use and clear definitions of terms like “digital twin,” “virtual population,” “uncertainty,” and “variability.”
Overlap with existing guidelines: Need to clarify relationship with PBPK and ICH M15 guidelines to avoid confusion.

Model Evaluation, Uncertainty & Data

Model Evaluation: Questions around “generic” best practices for model development, qualification, and validation across all types of mechanistic models. Suggestions to include examples and a risk-tiered framework to model evaluation.
Identifiability: Discussion on the importance and feasibility of parameter and structural identifiability, especially for large-scale models. Examples would be helpful to understand how this should be addressed for different types of mechanistic models.
Uncertainty vs. Variability: Strong call to distinguish and systematically address both; uncertainty (knowledge gaps) vs. variability (population heterogeneity).
Data Quality: Importance of using relevant, high-quality data, with transparent justification for data selection and handling of missing or disparate data.

Exploration of systematic use of study data to support regulatory assessment and decision-making

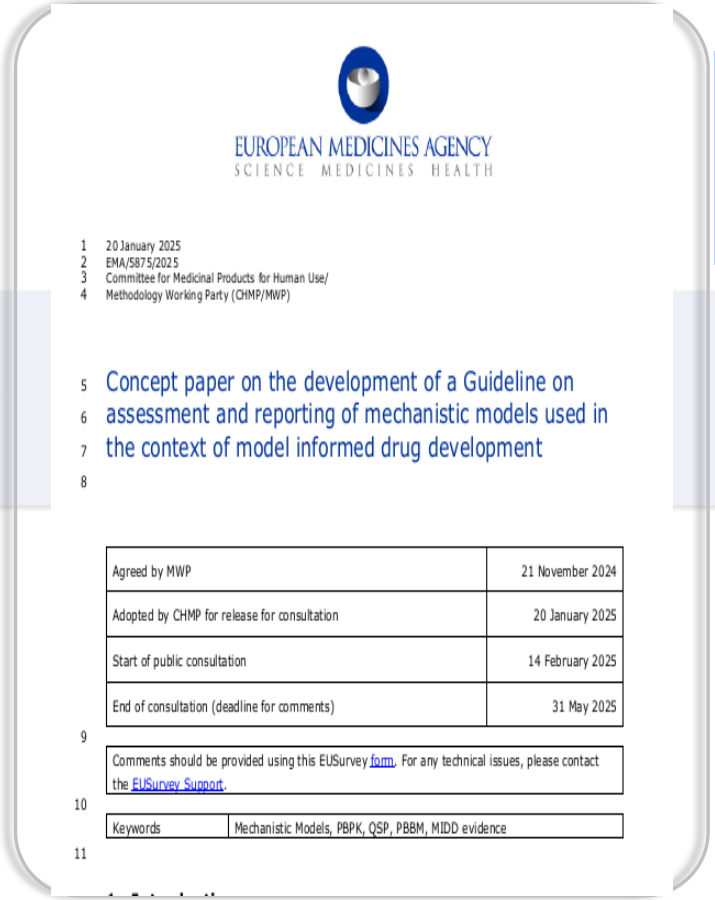
Reporting, Reproducibility & Regulatory Submission

Reporting Standards: Request for clear guidance on reporting model building, calibration, validation, and application, tailored to context and model type. Alignment with risk-based approach per ICH M15 may be needed.
Reproducibility: Emphasis on submission requirements to ensure reproducibility and transparency of models and simulations.
Regulatory Pathways: Guidance needed on when and how to consult with agencies regarding model use and supporting data.

Regulatory interactions, Stakeholder Engagement, Ethics, Other

Stakeholder Engagement: Calls for multidisciplinary drafting groups and clarification of the intended audience (regulators, industry, ethics committees).
Proposals to explicitly **include QST**, clarify extrapolation practices, and provide specific guidance on model diagnostics
Suggestion to include **case studies** and appendices for specific modeling approaches and regulatory scenarios (e.g. to support 3Rs principle).
Ethical Considerations: Highlight the importance of data quality principles (FAIR/CARE), transparency, and the 3Rs (animal testing reduction).

Toward the New Guideline on assessment and reporting of mechanistic models



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Public consultation:
14 Feb. 2025 - 31 May 2025
172 comments
from 10 stakeholders

EMA multi-stakeholder workshop on reporting and qualification of mechanistic models for regulatory assessment

8 – 9 October 2025

Hybrid meeting - Room 1C/ Webex, EMA, Amsterdam

Guideline on assessment and reporting of mechanistic models

https://www.ema.europa.eu/en/guideline-assessment-reporting-mechanistic-models-used-context-model-informed-drug-development#related-content-74226

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Thank you

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