EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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

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

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

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

1. Introduction

Mechanistic models, i.e. mathematical or computer models that integrate biopharmaceutical, physico-mechanical, (patho)physiological and pharmacological processes, along with population characteristics, are frequently and increasingly used in all phases of the drug research and development life cycle. Mechanistic models covered by this new guideline include, but are not limited to, Physiologically Based Pharmacokinetic (PBPK), Physiologically Based Biopharmaceutics (PBBM) and Quantitative Systems Pharmacology (QSP) models.

A PBPK model is a mathematical model that simulates the concentration of a drug over time in tissue(s) and blood, by considering the rate of the drug's absorption into the body, distribution in tissues, metabolism and excretion (ADME) based on interplay between physiological, physicochemical and biochemical determinants.

PBBM are a subset of PBPK models used to quantify the interplay between drug product (DP) quality attributes and the specification of clinically relevant limits for their quality control.

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

QSP models constitute a mechanistic modelling approach that is used to map the influence of therapeutic interventions on the disease-state or -trajectory. QSP models integrate molecular and cellular mechanisms of the disease and the drug into system-level dynamics, thereby providing a bridge between biomarkers and clinical endpoints relevant for the disease. Since they represent defined physiological pathways or biological mechanisms, QSP models are suited to understand the system-level response to treatment across multiple pharmacodynamic (PD) markers and clinical endpoints and to assess the mechanistic basis for patient variability.

In regulatory submissions mechanistic models have been proposed as a source of evidence to support assessment of comparability between formulations and between manufacturing processes, preclinical proof of concept (PoC), dose selection, study design optimisation, population enrichment strategies, extrapolation, benefit risk assessment and labelling.

The regulatory scrutiny and acceptance of evidence from model-informed drug development (MIDD) depends on the context of use, which ultimately defines the regulatory impact and associated risks. However, the inherent complexity of the mechanistic models as well as the type of data and methodologies used for their development and evaluation, mandate specific considerations for regulatory assessment and reporting compared to more empirical models, such as population pharmacokinetics, pharmacokinetic-pharmacodynamic and exposure-response models.

The only EMA guidance document on mechanistic models is the Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation, adopted by the CHMP in 2018 (EMA/CHMP/458101/2016).

To keep abreast with methodological developments in the field of MIDD, the scope of a new Guideline on assessment and reporting of mechanistic models applies not only to PBPK but also to other mechanistic models currently not covered by regulatory guidance documents, such as PBBM and QSP models.

2. Problem statement

Regulators should be able to confidently assess and quantify the potential risks associated with decisions based on mechanistic models, ensuring informed and accurate outcomes. However, due to the nature of these models, this is a non-trivial task and methods for uncertainty quantification are not well established within the current regulatory assessment framework. Moreover, key metrics and components for technical assessment and related acceptance criteria for mechanistic models, given the context of use and regulatory impact are not always clear which leads to their underuse or inappropriate use in drug development or/and poor communication between developers and regulators.

The following aspects are specific to mechanistic (QSP and PBPK/PBBM) models and currently not covered in any guideline:

- Mathematically, mechanistic models can have a complex structure and high number of interconnected parameters. This can potentially lead to issues related to structure identifiability that need to be adequately addressed.
- Mechanistic justification and plausibility of model structure and parameters, given the knowledge on human physiology and drug pharmacology is essential.
- Assumptions made related to model structure and parameters need to be justified.

- Data from different sources are used to inform parameter values: propagation of the uncertainty related to their quality and relevance on model predictive performance should be considered (i.e. uncertainty quantification).
- The tools used for assessment of model predictive performance need to be consistent with the intended use of the model. The relevance of the available data for model evaluation is particularly important.
- Virtual population generation (e.g. digital twins) and simulation scenarios should correspond to the intended use of the model.

3. Discussion (on the problem statement)

The following topics will be addressed:

- The different types and objectives of mechanistic models.
- Application of the MIDD evidence assessment framework on mechanistic models.
- Uncertainty quantification.
- Model structure and identifiability.
- Regulatory requirement for data quality and relevance.
- Model development and evaluation.
- Virtual population generation and simulation scenarios.
- Best practices for reporting of results of mechanistic modelling and simulation.

4. Recommendation

The Methodology Working Party (MWP) recommends drafting a guideline on assessment and reporting of mechanistic models used in the context of model informed drug development considering the issues identified above.

5. Proposed timetable

The concept paper will be published for a two-month public consultation period. The drafting of the guideline will start in 2025 with expected completion in 2026.

6. Resource requirements for preparation

The core drafting group will be a writing team of 4-6 people including clinical experts. A wider group of contributors is foreseen for discussion and review. The core drafting group will attend monthly meetings; the wider drafting group will convene bi-monthly.

A wider meeting is anticipated during guideline development with the MWP, its European Specialised Expert Community (ESEC) and designated internal stakeholders. A public EMA workshop on mechanistic modelling is planned in 2025. A webinar with external stakeholders at the end of the draft guideline writing process is considered.

7. Impact assessment (anticipated)

It is anticipated that this Guideline by setting regulatory standards for reporting and evaluation of mechanistic models will improve generation, communication and regulatory assessment of related MIDD evidence.

8. Interested parties

CHMP and its working parties, especially the Scientific Advice Working Party (SAWP), are the two main regulatory stakeholders that will be highly affected by this Guideline. Other regulatory stakeholders, which will likely be affected differently, are, the Paediatric Committee (PDCO), the Quality working party (QWP), Biologics working party (BWP), Quality Innovation Group (QIG), Non-clinical Working Party (NcWP), 3Rs Working Party (3RsWP) and the Committee for Orphan Medicinal Products (COMP). The aforementioned stakeholders will be consulted prior to releasing the draft to the public.

The Guideline will also benefit from the input of other regulatory agencies (e.g. FDA, PMDA, HC).

9. References to literature, guidelines, etc.

ICH M15 GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG DEVELOPMENT
ICH_M15_EWG_Step2_DraftGuideline_2024_1031.pdf
Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (europa.eu) ((EMA/CHMP/458101/2016))
MWP Workplan (EMA/CHMP/478317/2023)