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

Summary report from the meeting and follow-up activities

15th Industry stakeholder platform on research and development support

Workshop organisation

- 2-day workshop (8-9 October 2025)

- 80 participants F2F; 61-69 participants on MS Teams; ±400 views per day on livestream

- Day 1 chaired by Peter Arlett & Flora Musuamba; Day 2 chaired by Michael Berntgen & Flora Musuamba

- Presentations from members from EMRN, academia, EU Trade organisations (EFPIA, EuropaBio), platform developers (Certara, SimulationsPlus, OSP)

- Recording available on YouTube: https://youtu.be/UnI1doWOjMs (day 1); https://youtu.be/-jTlQiS6UWw (day 2)

Workshop objectives

- Share lessons learned from first qualification procedure for mechanistic models (Simcyp QO: https://www.ema.europa.eu/en/documents/other/qualification-opinion-simcyp-simulator_en.pdf) & understand stakeholder perception/plans on qualification initiatives

- Receive stakeholder feedback on methods for uncertainty quantification to support regulatory qualification

- Discuss feasibility/added value for future qualification of "other types" of mechanistic models (e.g. PBBM; QSP/QST)

- Review available GLs in the area & planned GL activities

Session 1 - Actionable Insights

The qualification of mechanistic models through the EMA qualification framework and beyond

➢ Clarify the distinction between **qualification** (broad design space, reserved to specific QoI, CoU and type of models) and **fit for purpose** (product specific, relies on MIDD strategic planning, and related evaluation activities)

➢ Clarify **EU paths** to acceptance of a mechanistic model

➢ Need for **early interaction** with regulators

➢ Work on "qualification" carried out by learned societies or industry consortia does not automatically result in regulatory qualification

➢ Policy is lacking on how to handle the **software life-cycle** (inter-version bridging)

➢ Need for **data-sharing** initiatives to support qualification activities

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Session 2 - Actionable Insights

Evaluation of predictive performance of mechanistic models for regulatory decision making: acceptance criteria, performance metrics, uncertainty quantification

- ➢ **Uncertainty Quantification** key for improving confidence in model-based decisions driving drug development and regulatory assessment

- ➢ **Bayesian meta-analysis**, as implemented in Simcyp qualification, was positively received

- ➢ Value of **hands-on data analysis** (by the QT) for improving the quality of the interaction with the model developers

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Session 3 - Actionable Insights

Mechanistic models for the future; challenges & opportunities in the context of Model-Informed Drug Development & risk assessment

➢ PBBM, PBPK, QSP/T are **rapidly advancing**, together with their regulatory applications

➢ QSP/T models widely used in R&D but **not always reported** to regulators

➢ QSP/T currently lack widely adopted community-driven best **practices and standards**

➢ **ICH M15** facilitates making mechanistic models a part of the MIDD toolbox

➢ Importance of **sharing data, model, and regulatory reviews**

➢ Need for **platform for early interaction** with regulators

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Session 4 - Actionable Insights

Regulatory guidance on mechanistic models, gaps & challenges in guidance documents

➢ Preference for **overarching mechanistic modelling GL** followed by method specific ones as annexes

➢ Model verification and validation, closely followed by UQ as key priorities for a GL

➢ Mechanistic modeling approaches vary in scientific and regulatory maturity, with PBPK being the most advanced, followed by PBBM and QSP

➢ Increase **transparency** in regulatory assessment of mechanistic models

Priority Actions Identified During the Workshop

Development Support	- Tailored MIDD SA and MIDD qualification procedures - Voluntary data submission framework for MIDD
Communication with Regulators	- Cluster TCs focused on mechanistic modelling - Explore opportunities for parallel MIDD advice with international regulators
Communication with Stakeholders	- Identify key industry stakeholders and outline strategic engagement plan - Publication in CPT
Guideline Activities	- Guidance on mechanistic models - Update EMA PBPK guideline with lessons from Simcyp QO - MIDD Qualification Q&A as annex to general qualification guidance

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Thank you

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