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

8 – 9 October 2025

In-person at the EMA building (Room 1C), Amsterdam + virtual enabled

Workshop Report

Disclaimer: This report is based on the materials and discussions of the mechanistic workshop available on the EMA website and should not be understood as the official views of the EMRN, EMA or its scientific committees or workshop participants.

Executive Summary

The HMA/EMA Multi-Stakeholder Workshop on Reporting and Qualification of Mechanistic Models for Regulatory Assessment was held on 8–9 October 2025, Amsterdam, in a hybrid format. The event convened approximately ±100 participants in person and ±300 participants online, representing regulatory agencies from across the EU network and internationally, pharmaceutical industry associations (EFPIA, EuropaBio), individual companies, academic institutions, scientific societies, and software platform developers. Workshop recordings and presentations were made available via the EMA website after the event.

The workshop addressed four objectives: to hear stakeholder views on the current regulatory framework for mechanistic model assessment; to share regulatory challenges with experts and stakeholders; to identify future qualification opportunities; and to define how the EU regulatory framework can be refined to streamline the use and assessment of mechanistic models. Proceedings were structured across four sessions covering (1) qualification of mechanistic models through the EMA framework and beyond; (2) evaluation of predictive performance, acceptance criteria, and uncertainty quantification; (3) mechanistic models for the future, including QSP/QST, agent-based modelling, PBPK in special populations, and virtual populations; and (4) regulatory guidance gaps, challenges, and international alignment.

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

Key recommendations that emerged from the workshop were:

- Establish a standing forum for strategic MIDD Agency-developer dialogue, including systematic horizon-scanning.
- Enhance regulatory-developer product specific interaction pathways with a focus on MIDD to enable early and iterative alignment on QoI, context of use, model risk and impact, evidence strategies, model evaluation and reporting requirements.
- Update relevant guidance to delineate platform qualification and model evaluation with explicit cross-references to the ICH M15 evidentiary framework.
- Enhance international regulatory communication and convergence on mechanistic modelling.
- Develop guidance on mechanistic modelling, ideally structured as a unified overarching guideline aligned with ICH M15 principles, accompanied by supplementary annexes addressing PBBM and QSP/QST.
- Revise the EMA PBPK guidance to reflect insights from a recently finalised qualification opinion and ensure alignment with ICH M15.
- Strengthen MIDD regulatory review transparency: Identify measures to enrich MIDD related content in EPARs and other public documents, thereby improving stakeholder understanding of the evidentiary basis and review considerations.
- Promote data sharing to strengthen collaborative qualification initiatives.
- Identify and leverage learned-society good-practice frameworks and reporting templates; where appropriate.
- Regulatory capacity and training on mechanistic M&S: Build on infrastructure and human resources and associated training curricula to advance assessment of MIDD evidence in regulatory submissions.

The discussions will directly inform priorities for EMA's qualification of novel methodologies programme and the development of new regulatory guidance on mechanistic models.

Workshop Proceedings: Day 1 — 8 October 2025

Opening Session

Day 1 Chairs: Peter Arlett (EMA) & Flora Musuamba Tshinanu (FAMHP)

The workshop was framed as a practical step to embed mechanistic modelling within the MIDD evidence base, aimed at faster, better-substantiated decisions across the medicinal products lifecycle and aligned with Agency and Network priorities (MWP and NDSG workplans). While anchored in general MIDD principles (ICH M15), mechanistic approaches have distinct features that deserve focused dialogue. Expectations for the workshop were: agreement on common versus model-type-specific assessment elements; clarity on optimal regulatory pathways; identification of scientific gaps; and clear positioning of the planned guideline relative to ICH M15.

Session 1: Qualification of Mechanistic Models Through the EMA Framework and Beyond

Chairs: Efthymios Manolis (EMA) & Carolien Versantvoort (MEB)

EU regulatory paths to acceptance of a mechanistic model— *Efthymios Manolis (EMA) & Carolien Versantvoort (MEB)*

Routes to acceptance include: case-by-case evaluation/Qualification within product applications ('fit-for-purpose' but resource-intensive and variable consistency); platform qualification via the EMA Qualification of Novel Methodologies (QoNM) procedure (efficient and reusable across compounds, albeit with only one example to date—Simcyp); and consortium-led qualifications published in the literature. The session aimed at discussing when and how platform qualification is relevant and applicable in new drug development.

Qualification of the Simcyp platform for CYP-mediated drug-drug interactions: a Certara perspective — *Karen Rowland Yeo (Certara)*

A 2.5-year, multi-party collaboration was described, culminating in EMA's first platform Qualification Opinion, which establishes a roadmap for more efficient PBPK platform qualifications.

It was highlighted that the context of use remains foundational, with credibility supported by robust system parameters, a targeted DDI qualification matrix, and explicit quantification of uncertainty.

Future priorities were outlined and included: CYP induction, CoU-4 scenarios without a clinical perpetrator DDI study, transporter-mediated DDIs, and applications in specific populations such as paediatrics, lactation, pregnancy, and organ impairment.

Software Verification, Validation, and Qualification of Open Source M&S Software for Regulatory Use in Translational Model-Informed Drug Development — *Stephan Schaller (Open Systems Pharmacology)*

Transparency by design was presented as essential—through public code, documented algorithms, automated testing, and multi-institutional validation—to establish trust in the absence of a universal qualification framework.

The OSP Suite and a community-driven context-of-use qualification approach were cited as practical enablers consistent with regulatory expectations.

Harmonization on PBPK platform and model qualification for regulatory assessment — *Viera Lukacova (Simulations Plus)*

Emphasis was placed on the importance of robust system equations, automated code verification, and a balanced qualification matrix as foundational elements. A delineation of responsibilities was proposed, whereby platform developers undertake platform qualification, sponsors validate models for their specific contexts of use, and strict version control is treated as essential.

Key challenges were identified, including platform-level risk assessment, inter-agency alignment, and clarity of processes, alongside the observation that qualification can streamline regulatory review for particular use-cases.

A Pharma industry PBPK perspective on the EMA qualification framework — *Neil Parrott (EFPIA)*

Three industry pathways were outlined—case-by-case assessments, EMA platform qualification, and cross-industry publications—along with a call for harmonised expectations to reduce duplication and improve predictability. Cross-industry initiatives were referenced in areas including CYP3A inhibition, organ impairment, and food effects. A recent qualification study focused on CYP3A induction was described as largely aligned with EMA platform qualification, with the exception of uncertainty quantification. The importance of leveraging cross-industry collaboration to support regulatory qualification was underscored.

Session 1 Panel Discussion

Additional panellists: Margareta Bego (HALMED), Alexander Kulesza (UNamur)

Panellists distinguished platform qualification from fit-for-purpose model evaluation, calling for clearer understanding of existing frameworks and stronger developer–regulator interactions around verification, validation and applicability (VVA). They emphasised that platform qualification is not the sole route to acceptance—new models can be accepted via risk-adapted VVA under ICH M15—although qualification can improve efficiency and consistency. Gaps identified included expectations for code submission and verification tools, assessment of automated processes, and timelines for qualifying platforms and contexts of use (CoUs); while the impact of the first platform qualification is still emerging, shorter timelines are anticipated. The panel also prioritised awareness and training (leveraging the qualification procedure/opinion, scientific advice, and targeted initiatives) and stressed that data quality, quantity, and sharing are critical; under the NPL framework, patient-level data submitted to EMA could support pooled datasets for future qualifications.

Session 1 continued

Holistic qualification of mechanistic models in drug development — *Jan-Frederik Schlender (OSP)*

It was argued that qualification delivers the greatest value for standardised applications, whereas many real-world cases—particularly in QSP—require model tailoring, with platform qualification serving a supportive role.

The importance of anchoring verification, validation, and applicability assessment (VVA) to the specific question of interest and context of use was emphasised, alongside maintaining sufficient platform flexibility to capture treatment-specific behaviour.

Qualification of the Simcyp platform: inter-version qualification bridging — *Masoud Jamei (Certara)*

It was noted that both the context of use and the EMA's Qualification Opinion are version-specific (v19), and that bridging to later versions requires transparency, quality assurance, traceability, reproducibility, and updated uncertainty quantification of predictive performance. It was also noted that updated analyses may be provided by either platform developers or end users as part of regulatory submissions.

Considerations for qualification of Physiologically Based Biopharmaceutics Models - Beyond the EMA framework — *Xavier Pepin (Simulations Plus)*

PBBM was presented as a means to avoid unnecessary studies across multiple questions of interest related to product quality and the interaction between altered physiology and formulations. Model quality and reliability were described as multifactorial, relying on robust platform verification (including sound equations and scientific rationale), platform qualification supported by sufficient high-quality datasets, integration of Chemistry, Manufacturing, and Controls (CMC) inputs and clinical data for validation, and strong practices and proficiency among developers and reviewers. It was highlighted that progress is often limited by sparse CMC and PK data, with curated public databases identified as potential accelerators.

Session 1 Panel Discussion

Additional Panellists: Jörg Lippert (Bayer), Victor Mangas (AEMPS), Scott Marshall (GSK)

Using ICH M15 terminology, panellists reviewed scenarios where platform qualification adds value. When models provide primary evidence, an available qualification can promote consistent assessments, facilitate acceptance, and focus review on additional data and model validation. Platform

Qualification could set a regulatory precedence that facilitates review and acceptance for similar platforms and applications. Across all scenarios, model risk and decision consequence remain case-specific.

Although regulators benefit from greater review efficiency and consistency, some participants questioned the developer return from platform qualification, noting the difficulty of aligning requirements with the diverse MIDD methodologies and accommodating the iterative, evolving character of development programs. To address this, early regulatory engagement—via standard scientific advice—was encouraged to align expectations and reduce uncertainty.

Platform qualification is not required and is not intended to address every MIDD application. Nevertheless, it delivers tangible industry value by qualifying the fundamentals, thereby building a credible foundation for discussion of new and more complex aspects. The panel also noted ethical benefits—for example, in organ-impairment settings, where model-based controls may reduce unnecessary human exposure—raising the question of when validated models could replace certain control arms. There are also scientific gains to be expected by the qualification process as shown in the Simcyp qualification opinion.

Participants discussed practical aspects of platform qualification, noting the expectation of a more streamlined (more lenient) qualification pathway following the first Qualification Opinion. They emphasised that platform qualification is a collaborative, iterative process with mutual learning and evolving requirements, and recommended requesting qualification advice early to reduce uncertainty before launching a request for qualification opinion. PBBM was identified as a near-term "low-hanging fruit" for selected contexts of use, while qualification of PBPK or more broadly MIDD approaches for PK scaling from adults to children was highlighted as an undertaking with significant impact for all stakeholders.

On transparency, the group stressed the need to improve understanding of PBPK regulatory assessments, urging greater MIDD assessment disclosure in EPARs and alignment with ICH M15 terminology. Regulators also debriefed on ongoing EMA transparency initiatives (e.g., EMA policy on Clinical Data Publication) and the upcoming ICH M15 implementation.

Session 2: Evaluation of Predictive Performance — Acceptance Criteria, Performance Metrics, and Uncertainty Quantification

Chairs: Pieter Colin (EMA) & Robin Svensson (MPA)

A regulatory perspective on performance verification of mechanistic models - application to PBPK-based DDI predictions — *Pieter Colin (EMA)*

An overview was provided of EMA's evolving approach to verifying the predictive performance of mechanistic models for platform qualification. It was explained that standard performance metrics are insufficient at the platform level because they do not account for heterogeneity in the quantity and quality of data across the qualification matrix, do not reflect that prediction uncertainty should depend on the context of use and the question of interest, and offer limited insight into the underlying properties of the platform model.

A Bayesian hierarchical meta-analysis developed in collaboration with Certara was described, which jointly estimated bias and imprecision in Simcyp DDI predictions across the qualification dataset and revealed substantive differences between mechanism-based and competitive inhibition drug-drug interactions (DDIs).

The resulting framework was shown to enable propagation of uncertainty parameters into actionable diagnostic tools for assessors, thereby directly linking platform-level qualification to regulatory decision making.

The adoption of model-based uncertainty quantification as the standard approach for future qualification exercises was encouraged.

Uncertainty quantification methods for complex models used in drug development and/or regulatory approval — *Andrew Hooker (CONFIRMS Consortium)*

A literature review of uncertainty quantification (UQ) methods was presented, identifying a broad range of approaches including global sensitivity analysis, Monte Carlo-based uncertainty propagation, Bayesian hierarchical meta-analysis, and profile likelihood methods.

In parallel, a screening conducted by the CONFIRMS consortium of European Public Assessment Reports and Scientific Advice Letters indicated that in 65% of EMA procedures involving mechanistic models UQ was addressed only briefly, and that in 46% of these cases the applied UQ methods were considered adequate.

A gap was identified between the current state of the science and prevailing regulatory practice. In response, it was noted that the CONFIRMS consortium, in collaboration with EMA, is developing a toolkit and accompanying tutorials to support the implementation of UQ in regulatory assessment and review.

Industry collective experience and discussion from a PBPK working group on the predictive performance of mechanistic PBPK model platform for specific PBPK applications — *Kunal Taskar (EFPIA)*

Collective industry experience in managing uncertainty for PBPK DDI applications was presented, highlighting the role of sensitivity analysis in uncertainty quantification alongside the current absence of detailed regulatory guidance and a uniform industry approach. Several use cases were discussed, including an industry-led initiative to qualify PBPK models for predicting oral contraceptive interactions and their application in DDI prediction. Disease-state effects on CYP enzymes and transporters were identified as a significant and insufficiently addressed source of uncertainty in DDI predictions for patient populations. A call was made, on behalf of the PBPK Modelling Working Group, to extend the qualification momentum established by the Simcyp Qualification Opinion to additional applications, such as enzyme induction, transporter-mediated DDIs, and special populations. The presentation concluded with an encouragement for closer regulator–industry collaboration to advance model-informed drug development.

Session 2 Panel Discussion

Additional panellists: *Paolo Rossato (EFPIA), Michael Chappell (Warwick University), Jörg Zinserling (BfArM)*

The Session 2 panel discussion generated substantive debate on uncertainty quantification methods and the role of structural identifiability. It was argued that conducting structural and practical identifiability analyses before parameter estimation should be considered a component of regulatory model qualification — a "think before you fit" discipline. This position was actively contested: arguing that requiring identifiability of all parameters would stifle innovation, particularly for QSP models where non-identifiable parameters are sometimes a feature rather than a flaw. The emerging consensus was that structural identifiability need not be a hard requirement, but that model reports should transparently disclose which parameters are non-identifiable and what impact this has on the model predictions. On UQ methods more broadly, it was agreed that the choice of approach must be stage-dependent and context-dependent: global sensitivity analysis may be appropriate in early development, Bayesian hierarchical modelling could be useful when rich qualification datasets exist, and worst-case scenario analysis is a pragmatic approach for complex cases with limited clinical data.

Future guidance on mechanistic models should explicitly acknowledge this spectrum of methods and specify the conditions under which each is appropriate.

Closing remarks Day 1

Peter Arlett (EMA)

Day 1 concluded with an emphasis on the tangible efficiency gains that platform qualification can deliver for both developers and regulators. Earlier, bi-directional engagement—via consortia and emerging collaborative pathways—was encouraged to align expectations sooner, alongside calls for capacity and capability building across EMA and its network to reinforce trust and strengthen evaluations of mechanistic models.

The use of established procedures, including ITF, scientific advice, and qualification advice, was recommended to de-risk development plans and supporting evidence packages. Greater transparency in the assessment of models within marketing authorisation applications was also encouraged so that insights can inform broader qualification activities.

Experience from the Simcyp qualification was cited, noting that hands-on regulatory analyses enhanced interactions and outcomes.

The importance of making uncertainty quantification an integral component was underscored, with reference to successful applications of Bayesian hierarchical meta-analysis in PBPK. Uncertainty quantification was identified as an ongoing regulatory science priority, supported by an EMA-funded study (CONFIRMS consortium) aimed at clarifying appropriate use of different approaches.

Finally, the central role of shared, high-quality datasets as a driver of collaboration was highlighted as a key focus for future efforts.

Workshop Proceedings: Day 2 — 9 October 2025

Opening and Day 1 Recap

Day 2 Chairs: Michael Berntgen (EMA) & Flora Musuamba Tshinanu (FAMHP)

Three strategic challenges framing the day's discussions were identified: ensuring model credibility and transparency across diverse platforms; addressing data limitations in special populations and rare diseases; and translating guidance into practice with sufficient clarity for both industry and regulators.

Four forward-looking themes from Day 1 were highlighted: continued discussion around the scope and return on investment of the QONM procedure; data sharing as a critical bottleneck; the existence of multiple regulatory pathways for model acceptance; and the need for regulators to adapt review approaches to the scale and complexity of multi-component mechanistic models.

Session 3: Mechanistic Models for the Future — Challenges and Opportunities

Chairs: Michael Berntgen (EMA) & Flora Musuamba Tshinanu (FAMHP)

An industry perspective on high impact QSP and QST model applications in clinical drug development in rare diseases — *Anna Sher (GSK)*

QSP was described as a form of mechanistic modelling that links target modulation to disease modification, positioning QSP models as central to drug development. These models support decision-making across all stages of the product lifecycle and are iteratively updated as new data and biological understanding emerge, reflecting their inherently dynamic nature.

Regulatory engagement with QSP has increased substantially, with submissions to the FDA rising from fewer than five per year in 2013 to more than 80 per year in 2023. Illustrative examples were referenced across a range of therapeutic areas, including cardiology, neurology, infectious diseases, and vaccines.

It was noted that, despite this growth, the field is still maturing, with outstanding technical questions and a standardised processes not yet available. The QSP ecosystem was also characterised as comparatively less transparent, with limited availability of open-source solutions and relatively little community-based peer review of models.

Close collaboration, improved communication, and stronger alignment among multidisciplinary teams across drug developers and regulators were identified as key priorities for advancing the field.

Experience with software platforms qualification for mechanistic models for agent-based modelling approaches — *Francesco Pappalardo (University of Catania)*

The Universal Immune System Simulator (UISS), an agent-based modelling (ABM) platform, was presented alongside a detailed account of its engagement with the EMA qualification advice procedure from 2021 to 2024, culminating in the issuance of a Letter of Support in February 2024.

The case study highlighted both the opportunities and the limitations of the current EMA framework when applied to novel model types.

A set of challenges specific to the UISS-TB-DR qualification process was identified, particularly in relation to credibility assessment, including validation strategy.

The need to include agent-based models in forthcoming EMA guidance was highlighted.

Opportunities for application of PBPK models in special populations and different modalities
— Loeckie De Zwart (EFPIA and EuropaBio)

A literature-based overview was presented on the evolution of PBPK applications beyond the established DDI context, extending into special populations and novel modalities. Illustrative case studies included paediatric DDI prediction in spinal muscular atrophy where clinical DDI studies are unethical, PBPK-informed dose adjustment in pregnant individuals with cystic fibrosis, and a PBPK model for an IgG drug product to predict tissue-level efficacy across indications.

It was noted that qualification maturity for these emerging applications has not yet reached the level achieved for DDI prediction. A key regulatory question was raised as to whether qualification considerations should differ when the context of use addresses unmet medical need.

The landscape of QSP modelling and Virtual Populations: From current to best practice—
Alexander Kulesza (ISoP QSP SIG)

It was emphasised that QSP models are diverse by design and that approaches to their assessment among stakeholders are still evolving. A working group on the credibility assessment of QSP for regulatory use was introduced, with the aim of compiling typical regulatory contexts of use and proposing guidance for assessing and reporting model credibility.

A credibility assessment framework was presented in the form of a pyramid, progressing from model and biological plausibility, through goodness of fit and calibration, to predictive performance and uncertainty, and ultimately regulatory readiness, with the relative importance of each element determined by the specific regulatory context of use.

The importance of harmonising terminology related to virtual patients was also highlighted, with a proposed distinction between (i) virtual subjects/patients, (ii) digital twins, and (iii) virtual populations composed of virtual subjects or digital twins, while recognising that each approach may require a distinct credibility assessment strategy.

Session 3 Panel Discussion

Additional panellists: Peter Theunissen, (MEB) Anne-Mette Hoberg (DKMA), Sathej Gopalakrishnan (EuropaBio), Saskia De Wildt (Radboud University Medical Center & Erasmus Medical Center), Elisabeth Wischnitzki (AGES)

The Session 3 panel discussion addressed the maturity of emerging model types and the role of academia. It was noted that PBPK models for older paediatric populations and pregnancy are approaching regulatory readiness, while data gaps remain for very young children. A structural concern was raised about academic QSP model development occurring without awareness of regulatory requirements, risking decades of modelling effort that would not be usable in a regulatory submission. Platform qualification for QSP was discussed as conceptually difficult given that EMA's procedure presupposes broader applicability across drugs — a condition rarely met by context-of-use-specific QSP models. Partial qualification of sub-modules was proposed as a possible intermediate approach. Transparency and the challenge of reviewing models with thousands of parameters were identified as fundamental issues requiring new approaches to regulatory dialogue.

Session 4: Regulatory Guidance on Mechanistic Models — Gaps, Challenges, and International Alignment

Session Chairs: Kristin Karlsson (MPA) & Francesca Day (EMA)

Guidance landscape—introduction — *Kristin Karlsson (MPA) & Francesca Day (EMA)*

The session opened with the presentation of ICH M15 as a unifying reference framework, setting the focus on priorities for the development of new guidance and the updating of existing guidance.

Guideline on assessment and reporting of mechanistic models used in the context of model informed drug development: Public comments received — *Flora Musuamba (FAMHP)*

Plans were outlined for an overarching guideline on mechanistic modelling aligned with ICH M15, covering terminology, verification, validation and applicability assessment (VVA), structural identifiability, uncertainty quantification, virtual populations, and reporting requirements, including code and data, with method-specific annexes.

Stakeholder feedback was discussed and called for a clearer scope, consistent terminology, explicit linkage to regulatory procedures, and the inclusion of method-specific annexes for approaches such as PBPK, PBBM, QSP, and QST.

Cross-industry feedback in implementation of regulatory guidance on mechanistic models: case studies, gaps, challenges and future perspectives — *Pradeep Sharma (EFPIA /EuropaBio)*

EMA's PBPK guideline was acknowledged for improving harmonisation, while remaining gaps were identified, including data requirements, acceptance criteria, treatment of digital twins and virtual populations, co-medication models, and the handling of large molecules and new modalities. Alignment of PBPK guidance with ICH M15 was encouraged, and the emergence of an industry-standard PBPK reporting framework was highlighted.

Support was expressed for an overarching guideline complemented by method-specific annexes, noting the relatively higher maturity of PBPK compared with PBBM and QSP.

PBBM Qualification and Guidance: Key Challenges and Emerging Opportunities — *Claire Mackie (EFPIA)*

Global momentum around the use of PBBM is building and is driven by multi-agency workshops and initiatives led by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ). Current applications span biopharmaceutics risk assessment, formulation design and development, drug-product quality, biowaiver strategies via virtual bioequivalence, and paediatric development using age-dependent absorption modelling.

Key challenges were identified, including complex parameterisation, model uncertainty, and the volume and quality of datasets required for verification and validation.

It was highlighted that there is an urgent need for: consistent terminology aligned with ICH M15; verification and validation standards tailored to the specific question and context of use; clearer interaction pathways prior to clinical trial authorisation (CTA) and marketing authorisation application (MAA); and closer collaboration between modelling working parties and quality assessors.

Shaping the Path Forward: Advancing Mechanistic Models for Regulatory Use — *Hao Zhu (FDA)*

PBPK and QSP were described as central components of many FDA reviews, alongside an emphasis on multidisciplinary collaboration and trust-building to address the technical challenges of model evaluation.

An example was cited from the review of olipudase Alpha, where a risk-based, comprehensive approach was applied to assess model performance.

Greater collaboration was found critical to strengthen the use of mechanistic modelling for evidence generation and regulatory decision-making.

Session 4 Panel discussion

Additional Panellists: Christer Tannergren (EFPIA), Michiel van den Heuvel (MEB), Elin Lindhagen (MPA), Sarem Sarem (HC), Shinichi Kijima (PMDA)

The panel examined how best to evolve guidance on mechanistic modelling and to align internationally across PBPK, PBBM and QSP/QST. Members agreed that the goal is not to over-prescribe, but to provide a clear communication framework that supports consistent, efficient assessments without hampering innovation. International regulators debated on whether new, method-specific guidance is needed now: PMDA saw no immediate need for dedicated QSP or PBBM guidance given the fields' immaturity and context specific application, while acknowledging PBPK guidance already exists and overarching guidance may be useful for communication; Health Canada argued for an overarching, high-level guideline supplemented by practical, method-specific annexes (e.g., PBPK, PBBM, QSP/QST) that define evaluation criteria and include examples.

All participants emphasized that any new text should be technically useful and inter-operational with existing guidance, and the group endorsed leveraging existing best-practice documents. At the same time, they cautioned that multiple templates/guidance can fragment practice, so harmonised terminology and complementary content are essential, with ICH M15 serving as the common reference point.

Against that backdrop, participants proposed targeted updates to EMA's PBPK guidance after the Simcyp qualification: keep the core intact but clarify qualification terminology (and expand the appendix on qualification), strengthen expectations for uncertainty reporting, and add illustrative case studies. Several noted that PBBM may ultimately merit a separate guideline.

Transparency featured prominently: the panel encouraged EMA to share more case examples and regulatory assessments (including richer EPAR content), pointed to FDA's comparatively open reviews, and urged new communication channels, peer-to-peer sharing of assessment reports, and mentoring to build capacity.

Finally, they called for regular industry–regulator fora to discuss next steps on guidance, best practices and templates, but also applications/methods that are mature or would benefit from qualification. Learned societies urged to spearhead good practices and standardised reporting, with regulators recognising and building upon those good-practice foundations.

Closing remarks Day 2 — *Flora Musuamba (FAMHP) & Michael Berntgen (EMA)*

The session concluded with an emphasis on early engagement through established pathways, including qualification, scientific advice, ITF, alongside the reminder that platform qualification is not the sole route to regulatory acceptance.

It was affirmed that discussions on mechanistic modelling guidance will continue, with an intent to capture common principles—such as credibility planning, verification/validation and uncertainty quantification, and lifecycle controls—within a single overarching guideline, supported by harmonised terminology and method-specific detail where appropriate.

The importance of early engagement, capacity building across the EU regulatory network, and international collaboration was reiterated.

It was also noted that the ongoing revision of the QoNM procedure and future priorities for EMA and EMRN will be informed by these discussions.