

28/05/2025

## 'Consultation: Development of a Guideline on Mechanistic Modelling.'

### Comments to Concept paper -

## "Development of a Guideline on assessment and reporting of mechanistic models used in the context of model informed drug development EMA/5875/2025"

### 1 Introduction

The VPH Institute appreciates EMA's initiative to draft a guideline on mechanistic modelling

As an international scientific society representing the professionals from academia, research institutes, hospitals and health technology assessment bodies with **expertise in *in silico* medicine**, we support the European Medicines Agency's consultation on the 'Guideline on the assessment and reporting of mechanistic models in the context of model informed drug development '.

In particular, we commend the European Medicines Agency's (EMA) Modelling and Working Party (MWP) for initiating the concept paper on **mechanistic modelling**. This proactive step directly aligns with the intentions outlined in the MWP's consolidated three-year workplan (2025-2027 (EMA-MWP, 2025)), released in February 2025. It's encouraging to see the Agency, through the MWP, acknowledge the need to advance **methodological excellence** across the EU regulatory network. Starting with this concept paper on modelling and simulation practice guidelines is a welcome move towards implementing this vision.

### 2 Comments and suggestions

#### Broader Scope and Expanded Applications of Mechanistic Modelling Guidelines

Building upon the valuable experience gained with physiologically based pharmacokinetic (PBPK) modelling and its associated reporting guideline (EMA, Guideline PBPK, 2016), the Agency's vision to foster similar advancements across a wider array of mechanistic modelling approaches is crucial. The EMA's initiative to release updated guidance on mechanistic modelling is highly commendable.

#### 2.1 Comment 1 - Introduction

##### 'Title: Guideline on assessment and reporting of mechanistic models'

**Observation (line 13-18):** The proposed guideline's title clearly signals the broadened scope, encompassing diverse mechanistic modelling techniques. This intent is further clarified in the introductory paragraph (lines 16-17), which explicitly states that the new guideline will include, but not be limited to, "PBPK, PBBM, and QSP modelling techniques."

**Suggestion (line 16-17):** While we strongly advocate for this inclusive approach to consider other model types, we recommend explicitly including agent-based, multi-scale, and multi-physics models in the scope of the guideline. Their mechanistic rigor and increasing use in regulatory science justify their recognition alongside PBPK, PBBM, and QSP (Curreli C. P. F., 2021). This would clarify the scope and help move beyond the typical application of modelling, which is now limited to investigation of pharmacokinetics, or pharmacodynamics primarily for dose-response estimations. This expansion will better equip the regulatory science community to reliably address the evolving needs for understanding complex disease progressions and the effects (intended or unintended) that new drugs have.

#### **Observation (line 19-31):**

Rightly following the concept paper's title, the introductory paragraphs (13-18) effectively establish a broad vision for the intended guideline.

**Suggestion (line 31-):** While the succinct descriptions of PBPK, PBBM, and QSP models (19-31) are appropriate, **we suggest including similar brief descriptions for other mechanistic models** that the guideline intends to cover. This would fully align with the expansive scope set out in the introduction.

We presume that the current description being limited to PBPK and QSP approaches might be due to the predominance of these models reviewed by the Agency, as well as their maturity, regulatory acceptance, and in-house expertise.

For your reference, our previous collaborations with EMA colleagues on '*Regulatory pathway of in silico methods for medicinal products* (Musuamba FT B. R., 2020), (Musuamba FT S. R., 2021)' have explored additional modelling approaches. **We are ready to further re-investigate, engage, and support with the descriptions and necessary details that best align with this new guideline.**

## 2.2 Comment 2 - Problem statement

#### **Observation on Problem statement (line 58-72)**

We fully understand and agree with the problem statement outlined by the EMA. We recognise the crucial need for regulators to confidently assess and quantify the potential risks associated with decisions based on mechanistic models. Furthermore, we acknowledge the necessity of due diligence in establishing robust methods for **uncertainty quantification** within the current regulatory framework, which is indeed a non-trivial task.

By proactively supporting and contributing to this consultation process with input from scientific experts, we aim to minimise the ambiguities that can lead to the underuse or inappropriate application of modelling approaches in drug development and assessment. This will, possibly support the guideline's intention to remove hurdles that hinder effective communication between developers and regulators.

#### **Observation on critical aspects (line 72-73):**

The list of critical aspects pertaining to mechanistic modelling, including the assumptions, data and tools is coherent. Additionally, the consideration of "Virtual population generation (e.g. digital twins)", as part of the critical aspects of mechanistic modelling, is indeed not considered elsewhere.

### **Suggestions (line 72-73): Integrating virtual populations and digital twins into mechanistic modelling guidelines**

As a scientific society actively spearheading the European vision for 'In Silico Trials with virtual population cohorts (Viceconti M. H.F., 2016)' and the use of 'Digital twins in healthcare (Viceconti M D. V., 2023)', we are eager to engage with the working party. **We seek to present relevant scientific evidence** on early adoptions previously identified with colleagues at EMA (Pappalardo F, 2019) and illustrative example cases, such as the 'Possible Contexts of Use for In silico Trials (Viceconti M E. L., 2021)'. Digital twin methodologies, particularly when combined with virtual populations, have the potential to enhance individualized risk assessment and support extrapolation strategies in paediatrics and rare diseases.

The above knowledge and inputs would possibly help ensure that these innovative methodologies are appropriately reflected and leveraged in the guideline, to best support the agency's vision to foster integrated evidence sources to evaluate and minimise uncertainty in regulatory decision-making.

## **2.3 Comment 3 – Discussion**

**Line 76- 'Model types'** - here, we would like to **reiterate our previous comments that the discussion best covers a broad list of mechanistic models** in alignment with the introduction.

**Line 78 – 'Uncertainty quantification'** – Needless to state, this is an active area of interest for the academic community, as we all seek this as a critical pillar to advance regulatory science on modelling and simulation.

To address the credibility of computational models, our colleagues are proactively engaged across sectors (drugs, devices, biologics), regulatory geographies (EMA, FDA), standardisation bodies (ASME, ISO) and community of practice, to best examine the needs of academics, industry, clinical community and regulators. For example, we represent in EMA's methodological working party, sub-committees of ASME V&V40 for medical devices and [VVUQ 80–Verification, Validation, and Uncertainty Quantification in Computational Modeling of Pharmaceutical Products](#).

Building on these engagements, **we would like to bring our collective learnings and latest advancements to best meet the needs of the authors drafting this guideline**. Thus, we seek the opportunity to understand and address the concerns on 'uncertainty quantification' and seek to shape the pathway ahead.

**Line 82 – 'Virtual population generation and simulation scenarios'** : same as suggestions line 72-73.

### Line 83 – 'Best practices for reporting of results of mechanistic modelling and simulation' :

Regarding the best practices, we encourage the consideration of the community's proposal "[Towards Good Simulation Practice](#)". This grassroots work involving experts in academia, the medical industry, regulatory bodies and hospitals, has captured the essential elements for conducting credible in silico trials, which is published into an open-source book titled - 'Towards Good Simulation Practice - **Best Practices for the Use of Computational Modelling and Simulation in the Regulatory Process of Biomedical Products** (Viceconti M. L., 2024)', with review and forward from regulatory colleagues at U.S. FDA. We recommend the Guideline encourage early dialogue between developers and regulators on mechanistic model strategy, including the use of innovative models (e.g., digital twins, ABMs).

## 2.4 Comments 4 - Resource requirements

Line 96-98: We are eager to follow up on our comments by **actively participating in upcoming stakeholder outreach and consultation events**. We commit to gather necessary references and scientific evidence to make this resourceful for developers and regulators.

## 3 Conclusion and next steps

Ultimately, we believe and support the EMA MWP's overarching goal and the interest of colleagues of other working parties, to best leverage **modelling and simulation alongside artificial intelligence (AI)**. This will essentially enable the **realisation of a quantitative assessment framework that effectively helps evaluate uncertainty when integrating multiple sources of evidence, ensuring that no single evidence source is arbitrarily favoured**.

Our comments on the proposed outline of these guidelines aim to support the EMA's commitment to engaging the community in producing **credible model-based evidence**. We readily agree that this evidence is crucial for robustly supporting the development and regulatory assessment of medicinal products throughout their lifecycle.

To conclude, **we fully acknowledge the need for caution and careful consideration of the implications as we seek changes. We look forward to constructively engaging with all stakeholder groups during the consultation process**. Our goal is to present evidence, address concerns, and support the European Medicine's Agency's collaborative efforts. We stand ready to leverage **Computational Modelling and Simulation (CM&S)** technology as a key enabler to advance the Model Informed Drug Development initiatives. By embedding scientifically sound and operationally feasible standards in this guideline, EMA can position the EU as a global leader in the regulatory use of mechanistic models.

## 4 References

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