Cross-industry Feedback in Implementation of Regulatory Guidance on Mechanistic Models: Case Studies, Gaps, Challenges and Future Perspectives

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Session 4: Regulatory guidance on mechanistic models, gaps & challenges in guidance documents

Acknowledgments

EFPIA pharma industry PBPK expert team

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The presentation represents the collected experience and opinions of multiple Pharmaceutical Industry experts in PBPK modelling who have united efforts for the purpose of delivering optimal input to this meeting.

The discussions were facilitated by the Simcyp Consortium Members Discussion Group (SMDG)

Final application and coordination was facilitated via EFPIA

We appreciate the opportunity to participate in this EMA multi-stakeholder workshop and thank the organizers for their work

- Introduction: Scope of Existing EMA PBPK Guidance
- Cross-industry Response to EMA Guidance
- Post-hoc Analysis of PBPK Submissions and EMA Guidance
- Identifying Gaps: Industry perspectives
- EMA Concept Paper Topics
- Conclusions

EMA Guideline On PBPK Modelling & Simulation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	***pharmacokinetics, modelling, simulation, qualification, predictive performance***

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Guideline aims to:

Describe the expected content of PBPK modelling and simulation reports

Documentation needed to support the qualification of PBPK platform for the intended use and the evaluation of the drug model

Cross-industry Response to EMA Guidance

1. Cross-industry Initiatives To Harmonise PBPK Reporting Templates

Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective

Mohamad Shebley[1], Punam Sandhu[2], Arian Emami Riedmaier[1], Masoud Jamei[3], Rangaraj Narayanan[4], Aarti Patel[5], Sheila Annie Peters[6], Venkatesh Pilla Reddy[7], Ming Zheng[8], Loeckie de Zwart[9], Maud Beneton[10], Francois Bouzom[11], Jun Chen[12], Yuan Chen[13], Yumi Cleary[14], Christiane Collins[15], Gemma L. Dickinson[16], Nassim Djebli[12], Heidi J. Einolf[17], Iain Gardner[3], Felix Huth[18], Faraz Kazmi[9], Feras Khalil[19], Jing Lin[20], Aleksandrs Odinecs[21], Chirag Patel[22], Haojing Rong[23], Edgar Schuck[24], Pradeep Sharma[7], Shu-Pei Wu[25], Yang Xu[26], Shinji Yamazaki[27], Kenta Yoshida[13] and Malcolm Rowland[28]

Source: Shebley M et al. Clin Pharmacol Ther. 2018 Jul;104(1):88-110. doi: 10.1002/cpt.1013. PMID: 29315504

Development of a Physiologically Based Biopharmaceutics Model Report Template: Considerations for Improved Quality in View of Regulatory Submissions

Published as part of Molecular Pharmaceutics special issue "2023 PBBM Workshop for Drug Product Quality".

Sumit Arora,* Xavier Pepin, Masoud Jamei, Pradeep Sharma, Tycho Heimbach, Christian Wagner, Philip Bransford, Sivacharan Kollipara, Tausif Ahmed, Martin Hingle, André Dallmann, Megerle Scherholz, Stephen D. Stamatis, Mario Cano-Vega, Nena Mistry, Christer Tannergren, Luiza Borges, Anders Lindahl, Gregory Rullo, Claire Mackie, Amitava Mitra, Joseph Kushner, Krutika Meena Harish Jain, and James E. Polli

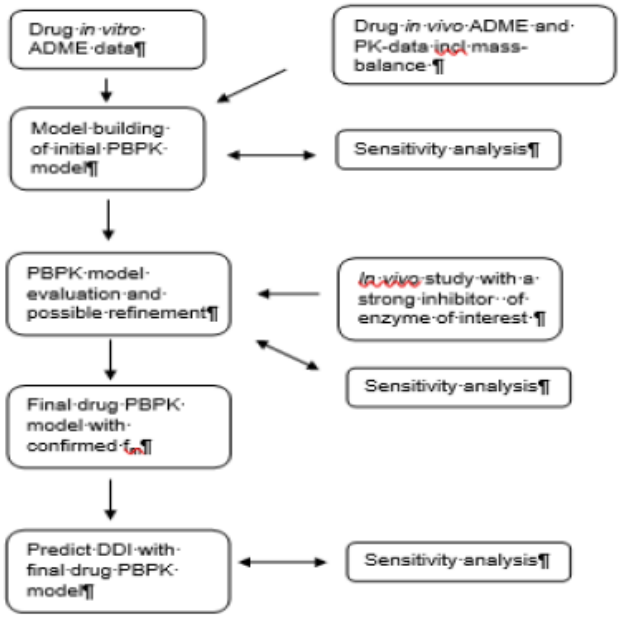
Source Arora S et al. Mol Pharm. 2025 Jun 2;22(6):2735-2746. doi: 10.1021/acs.molpharmaceut.5c00225. Epub 2025 Apr 29. PMID: 40300064

Emergence of fundamental PBPK reporting template with flexibility to adapt to meet specific requirements of mechanistic modelling approach and applications

Cross-industry Response to EMA Guidance

2. Stimulation of harmonisation of ways of working in industry establishing clearer workflow in model development, evaluation and application

Figure 2: Example of a DDI model: modelling workflow overview



Source: EMA PBPK Guidance 2019
https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation-scientific-guideline

- Implementation of fundamental basic workflow pathways
- Definitions of key terminologies
- Overarching regulatory expectations in model performance
- Emphasis to PBPK platform qualifications

EMA Guidance had been positively productive to advance regulatory sciences with growing needs of sponsors PBPK submissions

Post-hoc Analysis PBPK Submissions Post EMA Guidance

Current Use of Physiologically Based Pharmacokinetic modeling in New Medicinal Product Approvals at EMA

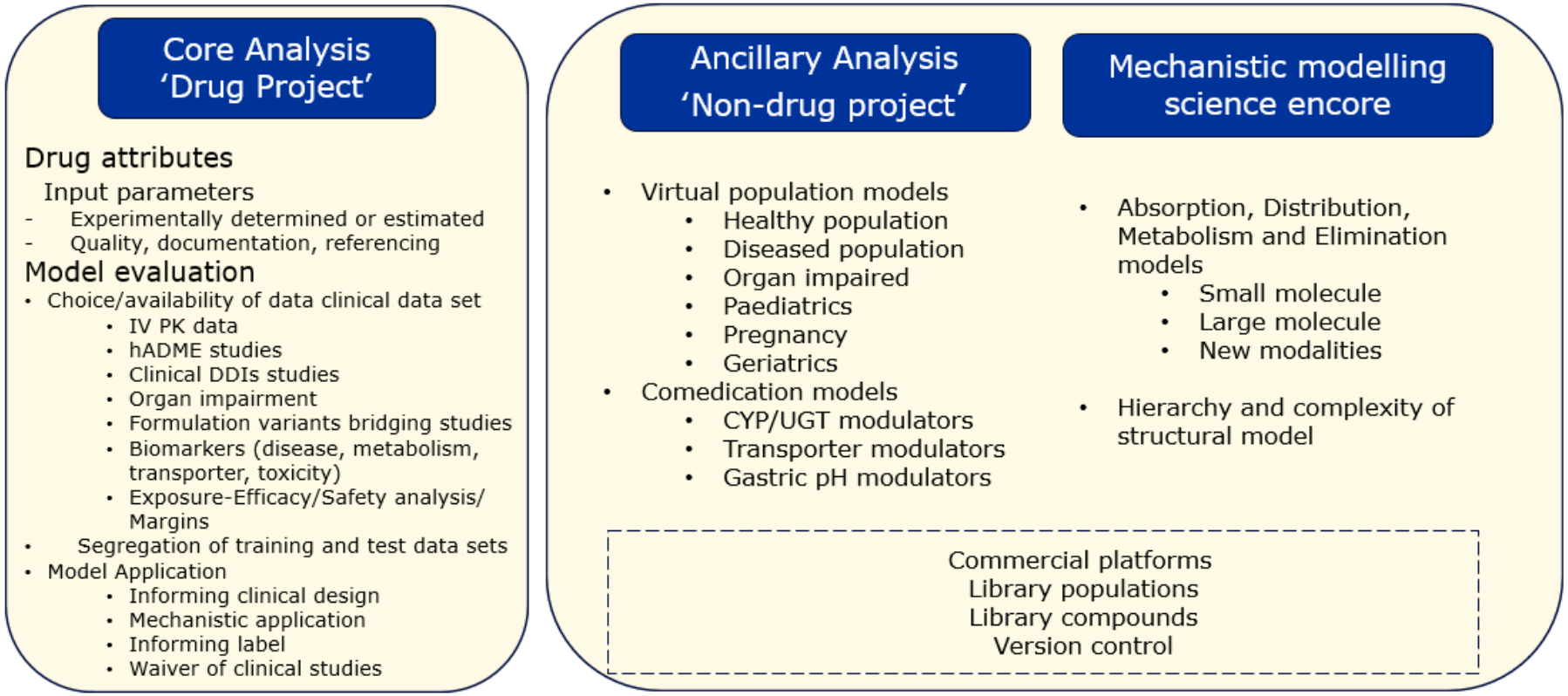
Polly Paul[1], Pieter J. Colin[1,2], Flora Musuamba Tshinanu[3,4], Carolien Versantvoort[5], Efthymios Manolis[1] and Kevin Blake[1,*]

Source: Paul P, Colin PJ, Clin Pharmacol Ther. 2025 Mar;117(3):808-817. doi: 10.1002/cpt.3525. Epub 2025 Jan 2. PMID: 39748538.

Need for further EMA guidance, particularly around requirements for qualification of PBPK models

- Approximately one out of four approved “full” applications contained PBPK modeling in 2022 and 2023 and 28% of these were considered qualified as per the EMA Guideline on the re-porting of PBPK modeling and simulation.
- Most of the models submitted in applications to EMA were not considered qualified for the intended use(s)
- Main reasons:
  - Concerns around PBPK structure
  - Lack of data to assess model’s predictive power
  - Poor prediction of clinical data
  - Insufficient justification of key assumptions (including key parameters)
  - In sufficient number of compounds in qualification data set
  - Reasons unclear from assessment report

Mechanistic Modelling: Deciphering Key Components



- Encore drug research companies/CROs
- Regular exercise in R&D

- 'Tools' for encore drug research activity
- Software vendors/ drug research companies/CROs

Current guidance is focussed on drug model and platform qualification

- What about virtual populations and digital twins?
- Do comedication models have different model validation requirements?
- Large molecules/new modalities specific guidance or case studies ?

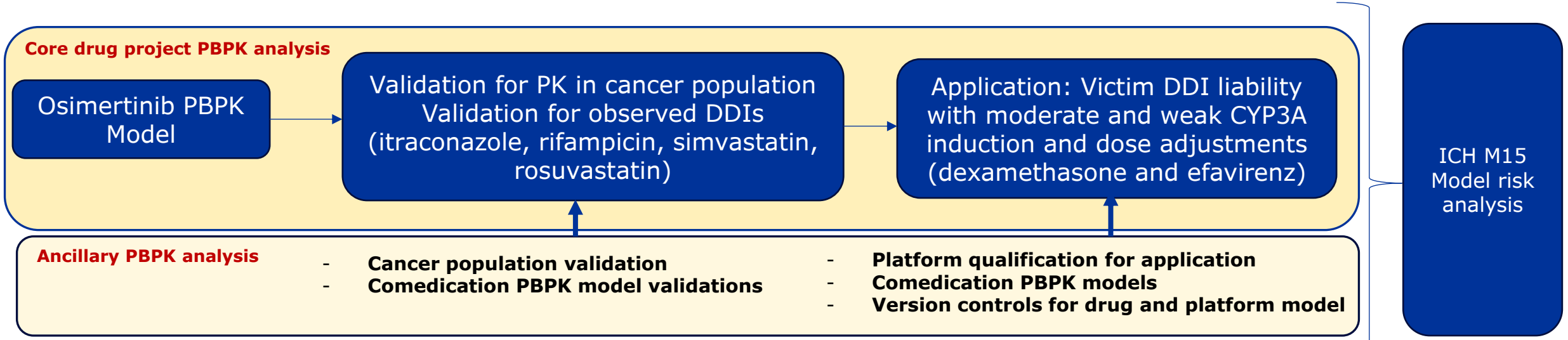
PBPK Analysis Reporting: Potential Challenges

Mechanistic modelling is time and resource intensive exercise. Is reporting ancillary PBPK analysis repetitive ?

Development, Verification, and Prediction of Osimertinib Drug–Drug Interactions Using PBPK Modeling Approach to Inform Drug Label

Venkatesh Pilla Reddy[1*], Michael Walker[1,6], Pradeep Sharma[2], Peter Ballard[3,5] and Karthick Vishwanathan[4]

Source: Pilla Reddy V et al, CPT Pharmacometrics Syst Pharmacol. 2018 May;7(5):321-330. doi: 10.1002/psp4.12289.



If commercial platform is used in industry, specifying platform version is enough to avoid rewriting population/comedication drug model validations?

Emerging Regulatory and Scientific Landscape and Adaptation of EMA Guidance

Cascading Impact of ICH M15 Guidance on EMA Guidance

Table 1: Guideline Overview: Sequence of MIDD in Relation to the Relevant Guideline Sections

Stages	Planning and Regulatory Interaction		Implementation, Reporting, and Submission		
Sequence of Activities	**Key Assessment Elements**	**Additional Considerations for Interaction with Regulator and to Inform Decision-Making**	**Model Evaluation**	**Model Analysis Reporting**	**Documentation for Regulatory Interactions and Submissions**
	• Question of Interest • Context of Use • Model Influence • Consequence of Wrong Decision • Model Risk • Model Impact	• Appropriateness of Proposed MIDD • Technical Criteria for model evaluation and model outcomes[1] These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation • Applicability assessment	• Model Analysis Report(s) (MAR)	• Regulatory documents, including + Outcome of MIDD Evidence Assessment + References to all relevant MAPs and MARs
Relevant Guideline Section	Section 2.1 and Appendix 1	Sections 2.2 and 4.1 and Appendix 1	Section 3	Section 4.2 and Appendix 2	Sections 2 and 4.3 and Appendix 1

Note: Terms used in this table are defined in relevant guideline sections.
[1] Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest.

Inform Decision-Making

- Ambiguity on how does EMA 'qualification' fits in ICH M15 model evaluation?
- Defining EMA's 'Regulatory impact' vis-a-vis ICH M15's 'Model Impact'
- Would 'model risk assessment' become part of reporting template?

EMA Concept Paper On Mechanistic Modelling

- Are the topics in the Concept Paper on mechanistic modelling well aligned with the identified gaps?
  - Structure identifiability
  - Mechanistic justification and plausibility of model structure and parameters
  - Assumptions
  - Uncertainty quantification
  - Clarification on assessment of model predictive performance
  - Virtual population generation

Yes, ‘high level recommendations’ and ‘best practices on above topics’ will bring more clarity / transparency and increased regulatory success

Ratiocination of Integrated Regulatory Guidance For Mechanistic Modelling Approaches: Pros and Cons

- Fundamental principles of mechanistic modelling are same e.g. workflows, techniques (parameter estimation) use of virtual populations. Specifics to methodologies QSP/QST(ODE, PDE, ABM), PBPK/PBBM can be added in Appendices
    - QSP/QST relying on extensive and diverse biomarker data and complex pathway models
    - PBBM requiring specifics of acceptance criteria to include inter and intrasubject variability
    - Agent based modelling as highly computationally intensive, and the process of calibrating parameters can be challenging often involving non-deterministic output
- Mechanistic modelling with interlinked methodologies e.g. ‘PBPK-QSP’ approach or PBBM application with inherent DDI risk (virtual bioequivalence of fixed dose combinations of interacting drugs) or complex non-linear PK
- Similar commercial software platforms are available on most mechanistic modelling approaches and can be applied interchangeably
- Different approaches are at different level of ‘scientific and regulatory maturity’. PBPK more advanced followed by PBBM and QSP in regulatory applications

QSP: Quantitative systems pharmacology; QST: Quantitative systems toxicology; ODE: Ordinary differential equations; PDE: Partial differential equations; ABM: Agent based modelling

Conclusions

EMA PBPK Guidance had positively impacted the application of mechanistic modelling in regulatory sciences

Further advancement / growth in modelling and simulation approaches, learning from post-hoc analysis of industry wide PBPK regulatory submissions and emergence of model risk assessment guidance are key drivers to refresh current guidance

Thank you

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BACK UPs

Mechanistic Modelling: Deciphering Key Components

Core Analysis 'Drug Project'

Drug attributes

Input parameters

- Experimentally determined or estimated
- Quality, documentation, referencing

Model evaluation

- Choice/availability of data clinical data set
  - IV PK data
  - hADME studies
  - Clinical DDIs studies
  - Organ impairment
  - Formulation variants bridging studies
  - Biomarkers (disease, metabolism, transporter, toxicity)
  - Exposure-Efficacy/Safety analysis/ Margins
- Segregation of training and test data sets
- Model Application
  - Informing clinical design
  - Mechanistic application
  - Informing label
  - Waiver of clinical studies

Ancillary Analysis 'Non-drug project'

- Virtual population models
  - Healthy population
  - Diseased population
  - Organ impaired
  - Paediatrics
  - Pregnancy
  - Geriatrics
- Comedication models
  - CYP/UGT modulators
  - Transporter modulators
  - Gastric pH modulators

Mechanistic modelling science encore

- Absorption, Distribution, Metabolism and Elimination models
  - Small molecule
  - Large molecule
  - New modalities
- Hierarchy and complexity of structural model

Commercial platforms
Library populations
Library compounds
Version control

Integrated Regulatory Guidance For Mechanistic Modelling Approaches: Pros and Cons

Pros

- Fundamental principles of mechanistic modelling are same e.g. workflows, techniques (parameter estimation) use of virtual populations
- Specifics to methodologies (QSP/QST/ PBPK/PBBM) can be added in Appendices
- Mechanistic modelling with interlinked methodologies e.g. 'PBPK-QSP' approach or PBBM application with inherent DDI risk (virtual bioequivalence of fixed dose combinations of interacting drugs) or complex non-linear PK
- Similar software platforms on most mechanistic modelling approaches

Cons

- Certain peculiarities exists for different mechanistic modelling approaches
  - QSP/QST relying on extensive and diverse biomarker data and complex pathway models
  - PBBM requiring specifics of acceptance criteria to include inter and intrasubject variability
- Different approaches are at different level of 'scientific and regulatory maturity'. PBPK more advanced followed by PBBM and QSP in regulatory applications