PBBM Qualification and Guidance: Key Challenges and Emerging Opportunities

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Agenda

- The Scientific Journey to date
- Use of PBBM in Innovator and Generic Industry
- Virtual Bioequivalence (VBE)
- Challenges & Opportunities
- Conclusions

PBBM: The Scientific Journey to date…

2017

Dissolution and Translational Modelling Strategies Enabling Patient Centric Product Development (MCERSI/FDA)

Developing Clinically Relevant Dissolution Specifications for Oral Drug Products (APS/EMA/MHRA

2019

Current State and Future Expectations of Translational Modelling Strategies to Support Drug Product Development, Manufacturing Changes and Controls (MCERSI/FDA)

2020

FDA Issues DRAFT Guidance On the Use of Physiologically Based Pharmacokinetic Analysis – Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes and Controls

2021

Developing Clinically Relevant Dissolution Specifications (CRDS) for Oral Drug Products: APS Virtual Webinar

IQ Consortium forms a work group to develop PBBM Case studies and selects 9 case studies

IQ Consortium PBBM group secures support from ANVISA, EMA, FDA, Health Canada and PMDA to independently and collaboratively assess the IQ case studies

2023

M-CERSI Workshop: Physiology Based Biopharmaceutics Modeling (PBBM): Best Practices for Drug Product Quality, Regulatory and Industry Perspectives: workshop

2024:

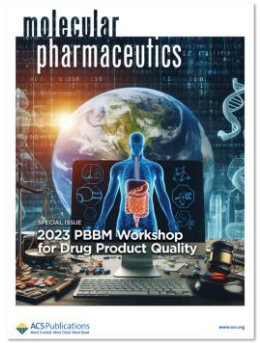
PBBM: Best Scientific Practices to Define Drug Product Performance: Latest Regulatory and Industry Perspectives (APS/MHRA as hosts)

ANVISA, Health Canada & PhRMA sponsored the ICH M15 PBBM Guideline/Annex Proposal

2025

EMA MIDD Concept Paper

ANVISA PBBM Draft Guideline



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6 Global Agencies discussing SCIENCE = momentum ☺

Scientific collaboration to advance quality medicines to patients

2-year path from September of 2021 to FDA/M-CERSI August 2023 workshop

Partnership

- Industry submitted confidential case studies
- Software companies commitment to training
- Academics agreed to participate
- Independently & collaboratively reviewed by regulators

IQ INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Case study	Company	Case study
1	Amgen	Amgen-Drug-x
2	Astrazeneca	Lesinurad
3	Astrazeneca	Acalabrutinib
4	EMD (Merck KGaA)	EMD-Drug-A
5	J&J	Janssen-Drug-A
6	J&J	Janssen-Drug-B
7	Merck & Co (MSD)	Etoricoxib
8	Novartis	Ribociclib
9	Pfizer	Fluconazole

64 FDA participants

16 Foreign Regulatory

22 Academics from around the world

85 Industry participants

187 In-person participants

- Regulators share thoughts in panel discussions
- 13 Breakout Sessions
- Workshop Output published – 5 manuscripts

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Use of PBBM in Innovator and Generic Industry

Biopharmaceutics Risk Assessment

Oral Drug Absorption assessment
Formulation platform prototyping

PPI/ARA/Food effects

Formulation design & development

Impact of API/excipient changes on DP
Formulation bridging

Biowaiver strategies based on VBE

Formulation bridging

Lower strength

Assessment between RLD & Test

SUPAC based

Drug Product Quality

Justification of clinically relevant drug product specifications:

API, Dissolution

*CMAs/CPPs based on safe space

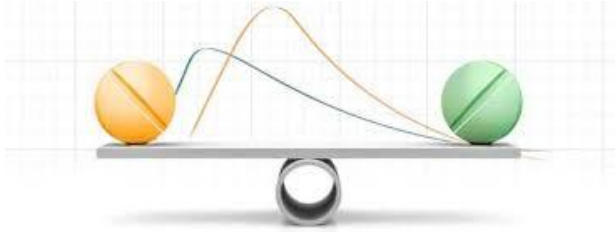
Paediatric Drug Development

Drug absorption as a function of age

rBA/BE studies to bridge to adult DP

* CMA/CPP: Critical Material Attribute/Critical Process Parameters

VBE - Virtual Bioequivalence



- VBE refers to the use of PBBM or PBPK modeling and simulation and other computational approaches to evaluate BE between drug products without the need for extensive in vivo clinical studies.
  - Evaluate the impact of CMC changes on the PK of the drug
- From a drug product quality standpoint, VBE:
  - Strengthens assurance of consistent clinical performance across formulations,
  - Facilitates efficient and cost-effective development, and
  - Reduces unnecessary human exposure, while maintaining alignment with regulatory requirement.

VBE - Virtual Bioequivalence

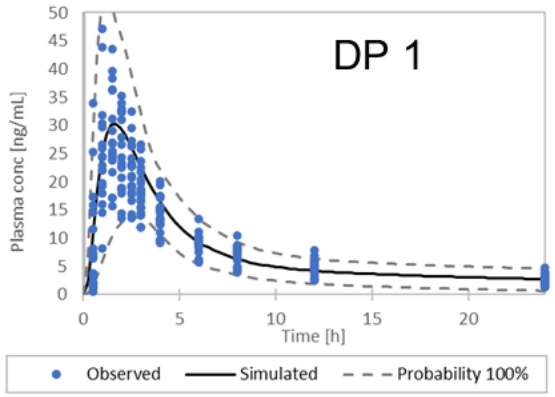
Areas of potential application

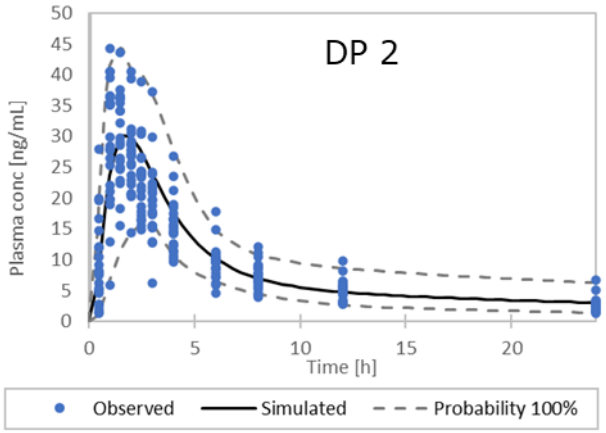
- **BE studies are often performed in 4 main areas**
  - Change in Manufacturing site (site switch)
  - Creating/introducing a new formulation
  - Introduction of a generic drug product
  - Biowaiver for lower strength(s)

- **Creating /introducing a new formulation can include studies to**
  - Bridge between 2 formulations
  - Evaluating the Food effect
  - Evaluate any PPI effect (the CMC DDI ☺)
  - Setting of Clinically Relevant Drug Product Specifications

VBE Example

- Model validation & VBE out come



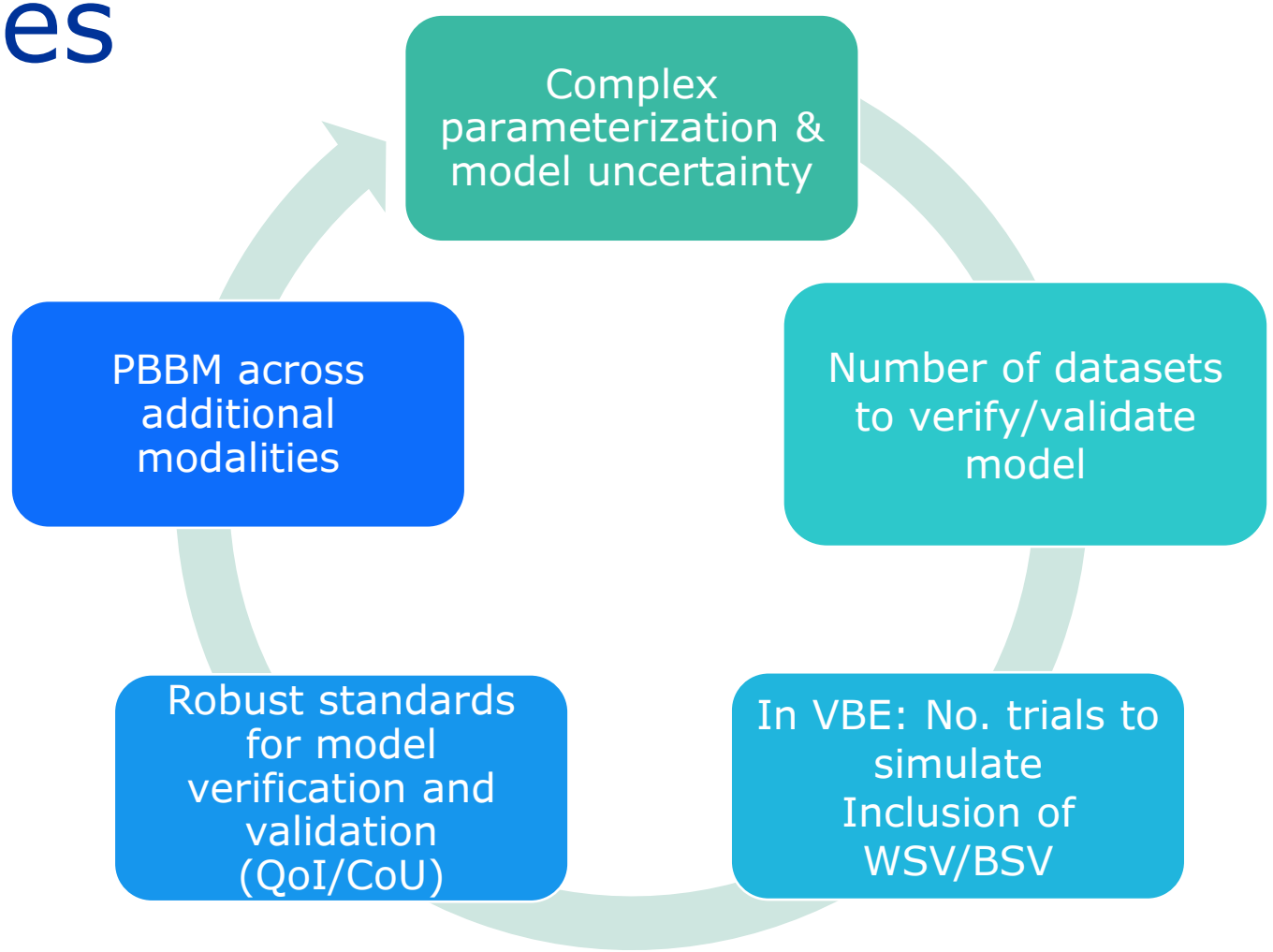


DP 1 vs DP 2	C_{max}		AUC_{inf}		BE Criteria
	GMR	90% CI GMR	GMR	90% CI GMR	
	[-]	[-]	[-]	[-]	[-]
Study 1	0.95	0.86-1.04	1.03	0.91-1.16	0.8-1.25
Study 2	0.96	0.87-1.05	1.04	0.93-1.16	0.8-1.25
Study 3	0.95	0.85-1.05	1.00	0.90-1.10	0.8-1.25
Study 4	1.04	0.92-1.17	1.03	0.91-1.17	0.8-1.25
Study 5	1.05	0.94-1.17	1.02	0.92-1.13	0.8-1.25
Study 6	1.06	0.97-1.17	0.98	0.86-1.12	0.8-1.25
Study 7	0.93	0.84-1.03	1.03	0.92-1.14	0.8-1.25
Study 8	1.05	0.96-1.16	0.97	0.86-1.09	0.8-1.25
Study 9	0.98	0.89-1.08	0.98	0.87-1.09	0.8-1.25
Study 10	1.05	0.96-1.15	0.99	0.90-1.08	0.8-1.25
Mean	1.00		1.01		

- **Steps in Model Build**
  - **Oral absorption model development: DS/DP**
  - **PK Model Development**
  - **Parameter Sensitivity Analysis**
  - **Model Validation**
    - **Independent clinical datasets**
  - **Model Application**
    - **Comparing different formulations through VBE**

- VBE trials demonstrate both drug products @ dose A are predicted to be BE for both C_{max} and AUC.
- A switch from DP1 to DP2 is predicted to have no impact on extend of absorption and exposure

Challenges



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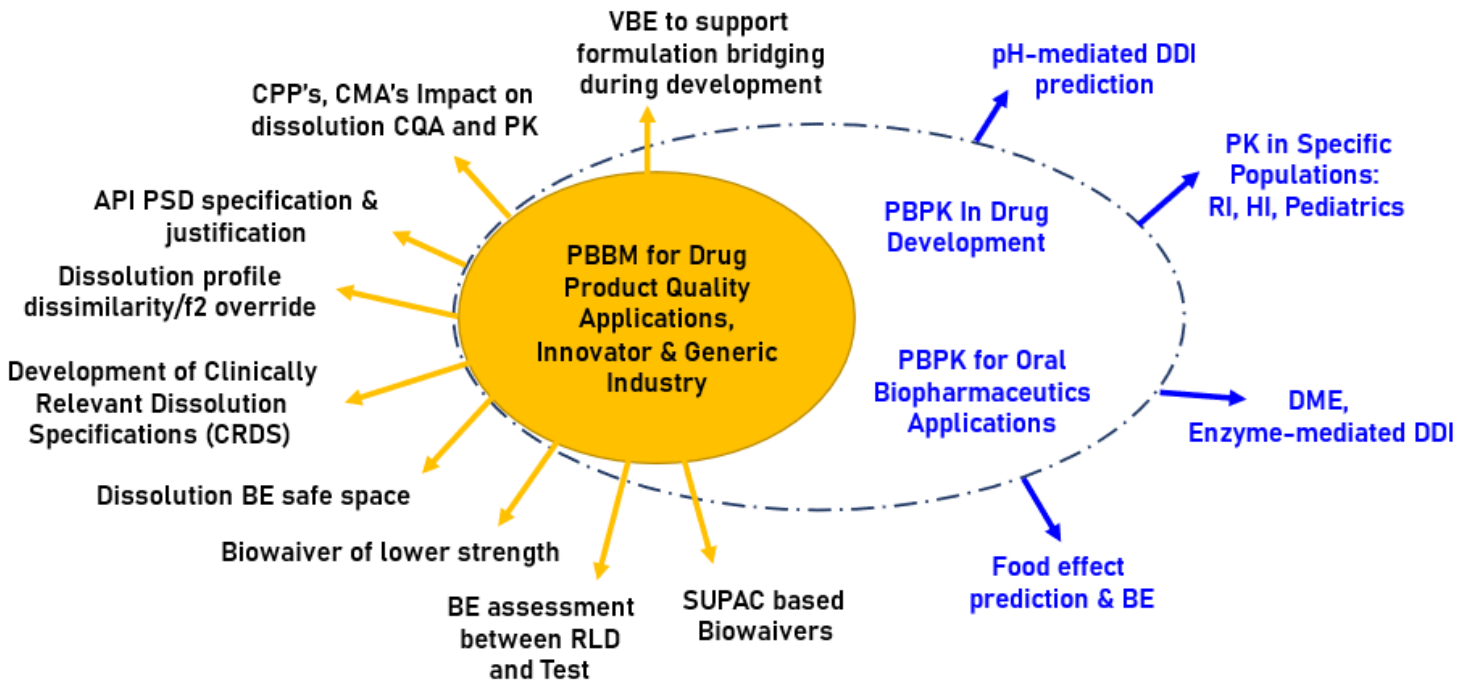
Opportunities

- Consistency in terminology across guidelines
- Clear process/mechanism to discuss modelling strategy (prior to CTA/MAA)
- Clarity on information required for strategic discussion
- Feedback on model “acceptability” in specification decisions
- Collaboration between MWP and Quality assessors in decision making



Uses of PBBM in oral formulation development. Adapted with permission from Yuvaneshwari et al. Copyright 2022, Elsevier

Conclusions

- Understanding biopharmaceutic attributes and API/DP interactions with the human body is essential across the product lifecycle
- PBBM improves drug product understanding by identifying critical formulation variables, Critical Material Attributes, and Critical Process Parameters
- PBBMs are central to MIDD offering robust, quantitative decision-making frameworks for regulatory decision making
- Consistent terminology aligned with ICH M15 on model development, verification, validation, and application are key for effective PBBM use
- PBBM's multidisciplinary nature means that Member State exposure and experience vary; EMA guidelines on mechanistic modelling could support broader adoption, and collaboration with industry and academics experts is encouraged
- Quality Assessors and the Methodology Working Party to collaborate to ensure consistency in decision making
- EFPIA aims to enhance the impact of PBBM across the product lifecycle through continued partnership with EMA and collaboration with industry, academia, and regulators

efpia
European Federation of Pharmaceutical Industries and Associations

Biopharmaceutics Modelling as a Fundamental Tool to Support Accelerated Access

Executive Summary

The acceleration of clinical development programs leads to the compression of the time available for the technical development of the Medicinal Product. Under these circumstances, CMC changes and bioequivalence studies to underwrite these, may affect the ability to rapidly deliver innovative medicines to the patients.

A deep understanding of fundamental biopharmaceutics properties of the active substance and product and the application of biopharmaceutics models beyond the BCS-based biowaivers are powerful tools in the acceleration of development programs.

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IQ

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