PBBM Applications to Support Regulatory Interactions

Luiza Novaes Borges

Health Surveilance and Regulation Specialist

Therapeutic Equivalence Department (CETER)

Brazilian Health Regulatory Agency (ANVISA)

ANVISA
Agência Nacional de Vigilância Sanitária

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent ANVISA's views or policies.

ANVISA
Agência Nacional de Vigilância Sanitária

PBBM Applications to Support Regulatory Interactions

Outline of presentation

1. BRIEF OVERVIEW OF PBBM MODELS

2. POTENCIAL APLICATIONS – DRUG DEVELOPMENT & REGULATORY DECISION MAKING

3. HIGHLIGHTS OF PBBM CASES SUBMITTED AND ASSESSED BY ANVISA

4. PBBM REGULATORY SCENARIO, INITIATIVES & PERSPECTIVES IN BRAZIL

PBBM Applications to Support Regulatory Interactions

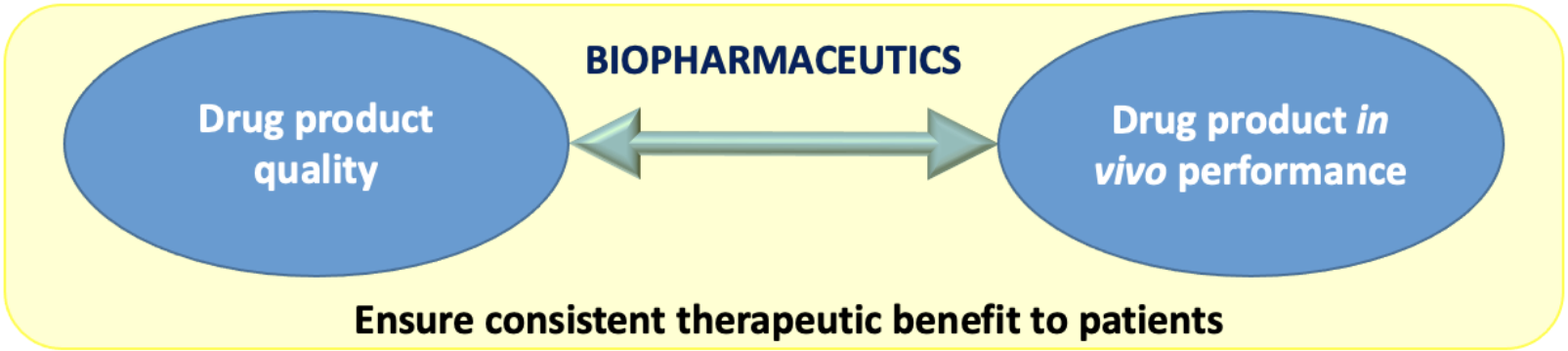
1. BRIEF OVERVIEW OF PBBM MODELS

Physiologically Based Biopharmaceutics Models (PBBM)

- Physiologically based models applied to biopharmaceutics assessments.

  - Biopharmaceutics is the study of the physicochemical properties of a drug and its dosage form as related to its bioavailability and pharmacokinetics.

  - Necessarily include **a mechanistic absorption model** (e.g.: ACAT – Advanced Compartmental Absorption Transit) = PBPK absorption + compartimental model, minimal or full PBPK



PBBM Applications to Support Regulatory Interactions

1. BRIEF OVERVIEW OF PBBM MODELS

PBBM focuses on providing **mechanistic understanding** of how drug product quality attributes interact with physiology influencing the *in vivo* drug performance.

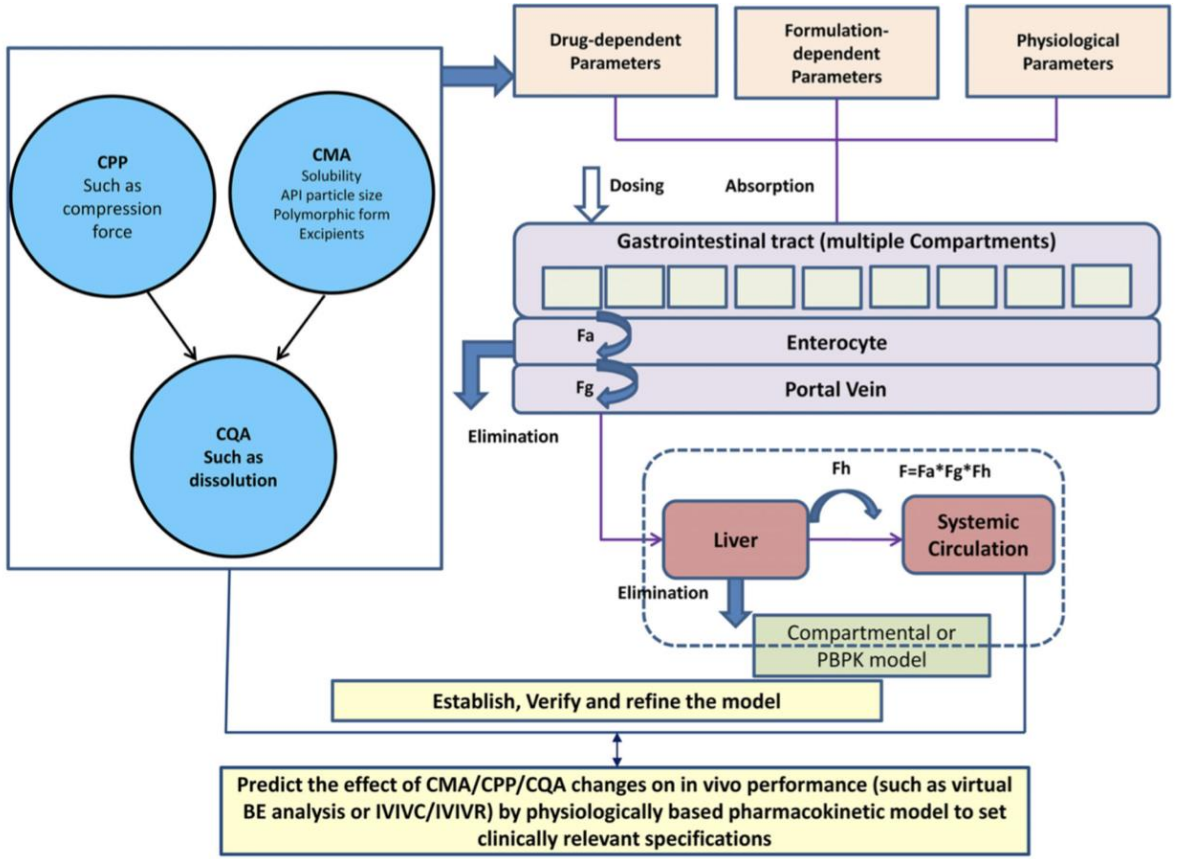


Fig. 4. General workflow for using PBPK modeling and simulation in biopharmaceutics assessment. Abbreviations: CPP, critical process parameters; CMA, critical material attributes; API, active pharmaceutical ingredient; CQA, critical quality attributes; F, oral bioavailability, Fa, fraction absorbed; Fg, bioavailability in the gut; Fh, bioavailability in the liver; BE, bioequivalence, IVIVC/R, in vitro in vivo correlation/ relationship

Wu F. et al. The AAPS Journal (2021) 23:31

PBBM Applications to Support Regulatory Interactions

2. POTENCIAL APLICATIONS – DRUG DEVELOPMENT & REGULATORY DECISION MAKING

Permits establish mechanist IVIVR/ IVIVC and/or perform virtual bioequivalence studies (VBE)

- Connect *in vitro* results (specially dissolution) to *in vivo* performance (normally as PK)

Unique relevance in biopharmaceutics arsenal to:

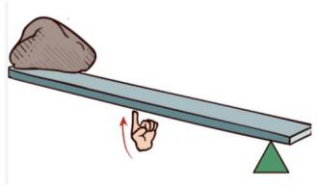
- Perform BE risk assessments
- Support biowaivers (BW)
- Set Patient-Centric Quality Standards (PCQS), like Clinically relevant drug product specifications (CRDP)

PBBM is an **evolving tool** which can be used throughout drug product development, regulatory approval, and life cycle management.

ANVISA
Agência Nacional de Vigilância Sanitária

2. POTENCIAL APLICATIONS – DRUG DEVELOPMENT & REGULATORY DECISION MAKING

For **drug product development**, PBBM as an enabler for QbD and MIDD principles incorporation:



- Enhanced knowledge about quality atributes that may affect absorption and PK (Critical Biovailability Attributes - CBAs)
- Optimize formulation development strategies
- Optimize biopharmaceutic assessment (e.g.: better design/ aboid a pilot BE study)

For **regulatory decision-making**, PBBM impact relates to the proposal risk level and the model credibility assessment:

IVIVR/C and safe spaces to:

- Support clinically relevant specifications for CBA (e.g.: dissolution, API particle size, % polymorphic forms)

Support BE risk assessment or BW for:

- Post-approval CMC/ SUPAC changes (e.g.: failed *in vitro* dissolution similarity test);
- Diferent strenghs with non-proportional formulations;
- BCS Class III drugs non quali-quantitatively the same (Q1/Q2);
- Food effect on BE;
- pH driven DDIs;
- Patients with altered GI physiology conditions.

PBBM Applications to Support Regulatory Interactions

3. CASES SUBMITTED TO ANVISA

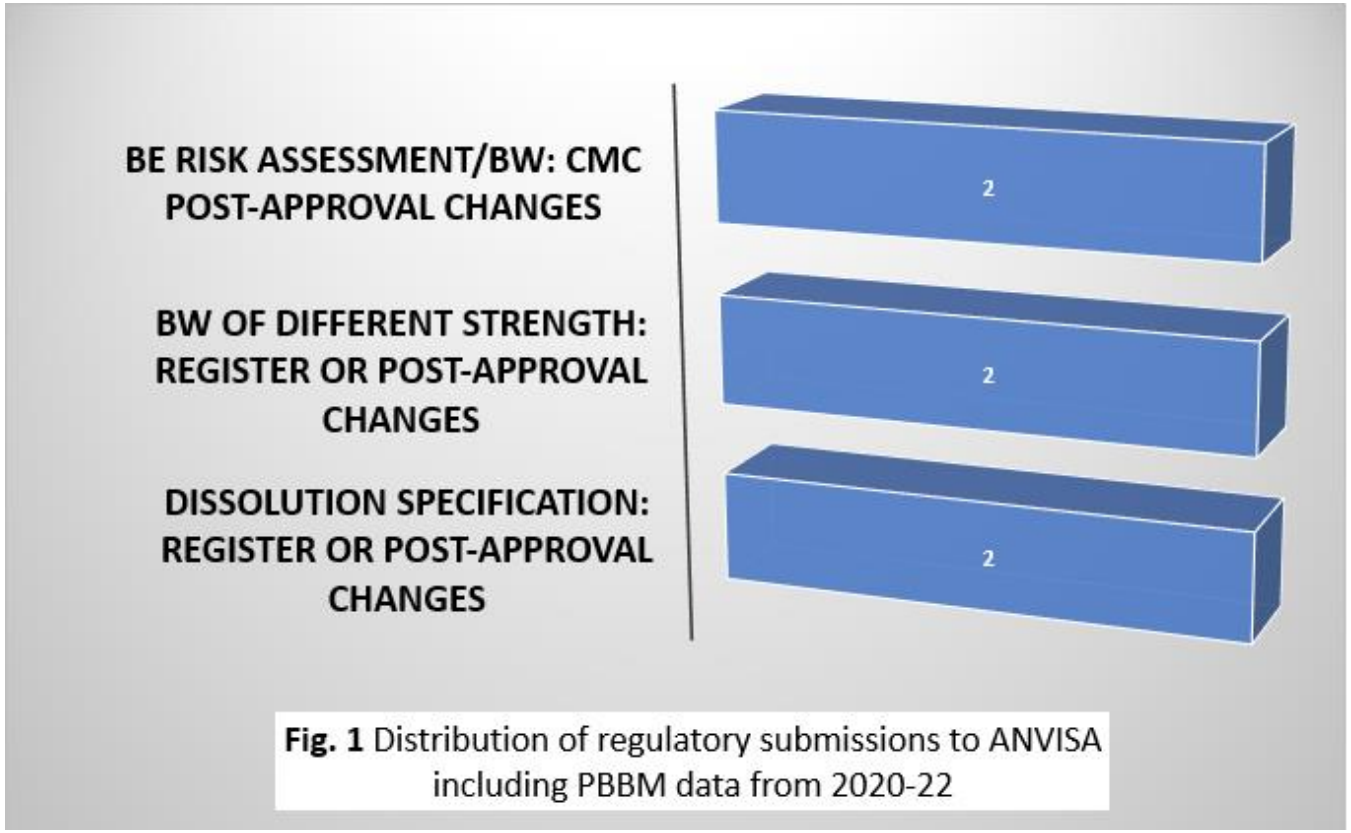


Fig. 1 Distribution of regulatory submissions to ANVISA including PBBM data from 2020-22

In preparation

ANVISA
Agência Nacional de Vigilância Sanitária

PBBM Applications to Support Regulatory Interactions

3. CASES SUBMITTED TO ANVISA

CASE Nº	APPLICATION CATEGORY	ISSUE / COMPANY	PROPOSAL	DOSAGE FORM / BCS	MAJOR ASSESSMENT POINTS/ ISSUES	REGULATORY DECISION
Case 1	NME – CMC post- approval major change *BE required	Failed F2 and Mahalanobis distance comparison on dissolution profiles	Mechanistic IVIVC to support BW	ER BCS III	Uncertainties in disposition (lack of IV data) Lack of experimental solubility data QC dissolution method were not bio-predictive (correlation equation and validation were not shown)	**Denied** Clinical BE studies required: fast and fed states
Case 2	NME – CMC post-approval change *BE not required	Failed F2, Mahalanobis distance and bootstrap F2 comparison on dissolution profiles	PBBM-VBE to support BE risk assessment	IR BCS IV	Precipitation risk assessment Rank order relationship of in vitro dissolution-PK and supportive IVIVC (relevant variants) Uncertainties in WSV and BSV incorporation	**Approved** i.e.: post-approval change approved based on model evidence (fit for this purpose)

In preparation

PBBM Applications to Support Regulatory Interactions

3. CASES SUBMITTED TO ANVISA

CASE Nº	APPLICATION CATEGORY	ISSUE / COMPANY	PROPOSAL	DOSAGE FORM / BCS	MAJOR ASSESSMENT POINTS/ ISSUES	REGULATORY DECISION
Case 3	Generic – BW of lower strength	Failed F2, despite being a proportional similar formulation to the higher strength	PBBM-VBE to support BW	IR BCS I/II (unstable in low pH)	Not enough knowledge about product CQAs Uncertainties in dissolution Lack of model validation (i.e.: different clinical dataset)	**Denied** Only higher strength registered as generic (BE based) Thorough quality investigation to support lower strength inclusion
Case 4	Generic – BW of higher strength	Failed F2, Mahalanobis distance, despite being a proportional similar formulation to the lower strength	PBBM-VBE to support BW	IR BCS II	Uncertainties in disposition (lack of IV data) API of high BSW and subject to dose dependent food effect DP-PSD as CQA (uncertainties in estimation)	**Withdrawn** BE study performed by company and showed a nBE result DP reformulation

In preparation

PBBM Applications to Support Regulatory Interactions

3. CASES SUBMITTED TO ANVISA

CASE Nº	APPLICATION CATEGORY	ISSUE / COMPANY	PROPOSAL	DOSAGE FORM / BCS	MAJOR ASSESSMENT POINTS/ ISSUES	REGULATORY DECISION
Case 5	NME – Post-approval change of dissolution specification	OOS results with approved CQ dissolution specification	PBBM-VBE to support new dissolution specification based on PBDT	IR BCS I	Uncertainties on integration of PBDT dissolution data Uncertainties in the relation between PBDT and CQ dissolution limits Uncertainties in WSV and BSV incorporation	**Approved** i.e.: post-approval change approved based on model evidence (fit for this purpose)
Case 6	NME – Risk assessment for dissolution specification approval	Justify the clinical relevance (PK&PD) of the dissolution specification	PBBM-SAFE SPACE/PK-PD to justify the clinical relevance of dissolution specification	IR BCS II	N/R - Model were developed for DP reformulation and other regulatory purposes	**Informative** i.e.: dissolution specification would be approved based on discriminating in vitro capacity

OOS – Out of specification; PBDT – Physiologically Based Dissolution Test; PK/PD – pharmacokinetic /pharmacodynamic

In preparation

PBBM Applications to Support Regulatory Interactions

4. PBBM REGULATORY SCENARIO, INITIATIVES & PERSPECTIVES IN BRAZIL

- PBBM acceptance for review on a case by case basis / meeting interactions: need of local M&S/ PBPK/ PBBM GL
- Mapping on alignment/amendments needed on current ANVISA regulations of related biopharmaceutic analysis: QbD, CMC/SUPAC changes, dissolution, IVIVC, BE/ BW
- Need to have biopharmaceutic risk assessment frameworks (for industry and regulator, e.g.: BioRAM Roadmap, FDA Biopharmaceutic Risk Categories and Decision Trees)
- Need of decision trees applied to some critical PBBM parameters/ steps (e.g.: solubility, precipitation, integration of dissolution, DP-PSD)

ANVISA
Agência Nacional de Vigilância Sanitária

PBBM Applications to Support Regulatory Interactions

4. PBBM REGULATORY SCENARIO, INITIATIVES & PERSPECTIVES IN BRAZIL

Scientific best practices - regulatory convergence – reliance pathways

Value of regulators – industry – software developers - academia collaborations!

- ✓ Training sections with GastroPlus for ANVISA team (set/20 – oct/21)
- ✓ IQ Consortium – Regulators PBBM Collaborative Study (invited on Ago/21, case submissions jun/22)
- ✓ WG on PBBM Best Scientific and Regulatory Practices – ANVISA and academia (working on 6 case studies)
- ✓ Gain experience with other relevant biopharmaceutics *in vitro* studies
- ✓ Gain experience with other software plataforms
- ✓ Strenght network/ presence in pharmacometric (e.g.: RedIF – Iberoamerican Pharmacometrics Network)

PBBM Applications to Support Regulatory Interactions

4. PBBM REGULATORY SCENARIO, INITIATIVES & PERSPECTIVES IN BRAZIL

Back to the Center for Excellence in Regulatory Science and Innovation

Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives

Registration

Mark your calendars to attend a workshop on Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives. The workshop is sponsored by the University of Maryland Center for Excellence in Regulatory science and innovation (M-CERSI) and the Food and Drug Administration (FDA).

Important Event Information	
Date:	August 29-31, 2023

WORKSHOP FOR BRAZILIAN AUDIENCE IN 2024

Best scientific and regulatory practices:

Biopharmaceutics *in vitro* studies/QbD implementation/ PBBM

Involve other stakeholders from ANVISA (bottom up and top down convergence for change!)

Involvement of local/ generic based industry and local academia experts

ANVISA
Agência Nacional de Vigilância Sanitária

Thank you for the attention!

luiza.borges@anvisa.gov.br

Anvisa

SIA Trecho 5 - Área especial 57 - Lote 200 -

CEP: 71205-050 - Brasília - DF

www.gov.br/anvisa

Central de Atendimento: 0800-642-9782

ANVISA
Agência Nacional de Vigilância Sanitária

Acknowledgements:

Reviewers from CETER (Therapeutic Equivalence) and GQMED (Register and Pos-approval quality) - WG on PBBM

Dr. Eduardo Agostinho Freitas Fernandes – Coordinator of CETER/ANVISA

SimulationPlus Team and Dr. Frederico Severino Martins

Profa. Andrea Diniz – University State of Maringá (UEM) - Brazil

Prof. Marcelo Dutra Duque - Universidade Federal de São Paulo (Unifesp) - Brazil

Profa. Natália Valadares de Moraes - University of Florida - USA

Profa. Sandra Elisa Haas – Federal University of Pampa (Unipampa) - Brazil

Dr. Greg Rullo - chair of IQ Consortium Subgroup in Control Strategy Harmonization for inviting ANVISA for collaborate