Applications of PBBM in regulatory submissions

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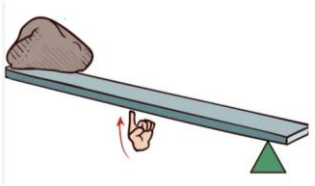
Outline of presentation

1. POTENCIAL APLICATIONS – DRUG DEVELOPMENT & REGULATORY DECISION MAKING

2. HIGHLIGHTS OF PBBM CASES SUBMITTED AND ASSESSED BY ANVISA

3. PBBM REGULATORY SCENARIO, INITIATIVES & PERSPECTIVES IN BRAZIL

1. 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 and dissolution development strategies
- Optimize biopharmaceutic assessment (e.g.: better design/ avoid pilot BE study)

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

IVIVR/C/E, safe spaces to and/or VBE:

- Support clinically relevant specifications for CBA (e.g.: dissolution, API particle size, % polymorphic forms)
- Post-approval CMC/ SUPAC changes (e.g.: failed *in vitro* dissolution similarity test);
- BE/BW diferent strenghs with non-proportional formulations;
- Food effect on BE;
- pH driven DDIs;
- Patients with altered GI physiology conditions.

2. CASES SUBMITTED TO ANVISA

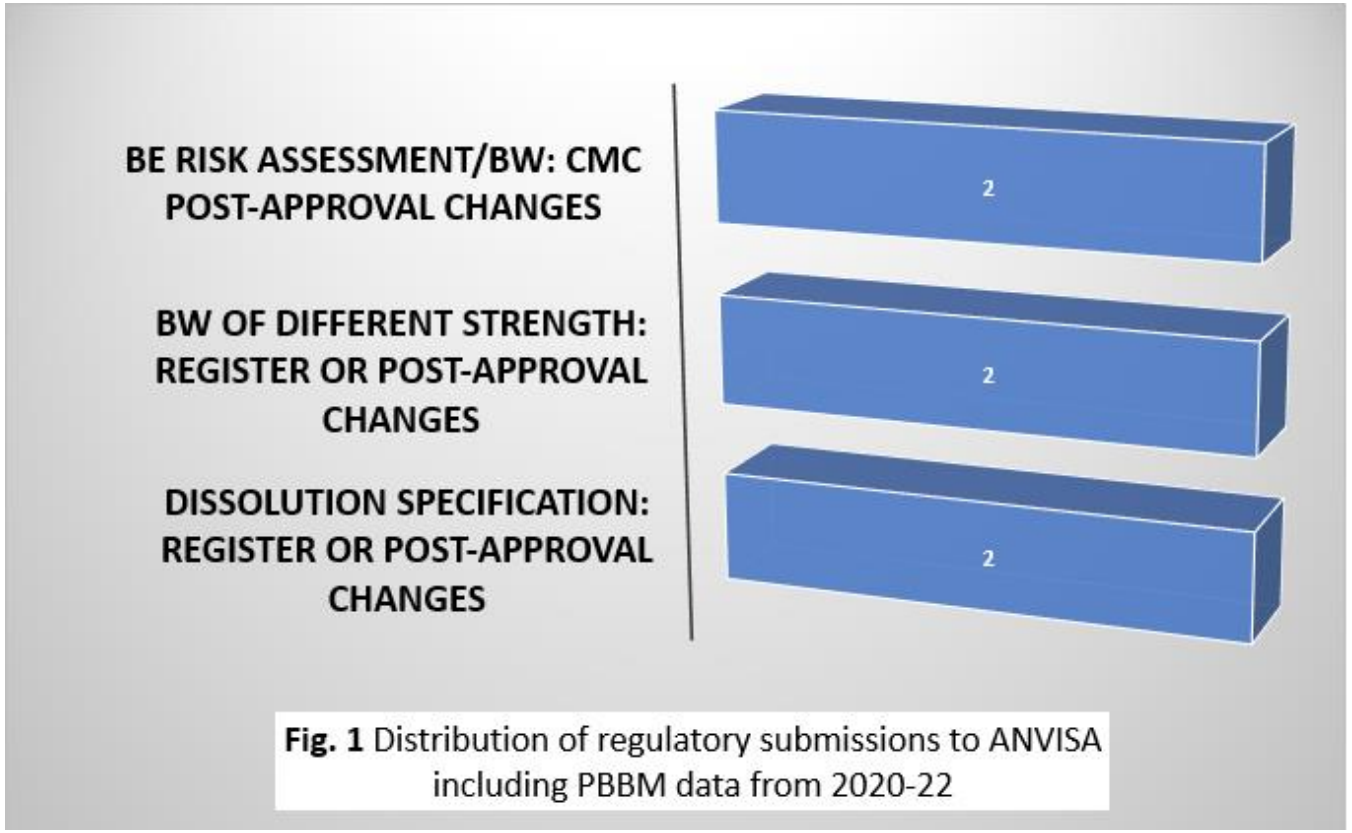


Fig. 1 Distribution of regulatory submissions to ANVISA including PBBM data from 2020-22

In preparation

To:

CETER (Therapeutic Equivalence Department) and GQMED (Office of Pharmaceutical Quality)

By:

National and multinational companies, for NME and generic drugs

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2. 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)

2. 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

2. 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

Value of regulators - industry - academia - software developers collaborations

Best scientific practices - regulatory convergence – reliance pathways

- ✓ Training sections with GastroPlus (2020-21) and Simcyp (2023)
- ✓ 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 (since Ago/22)

3. PBBM REGULATORY SCENARIO, INITIATIVES & PERSPECTIVES IN BRAZIL

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PORTARIA N° 627, DE 10 DE AGOSTO DE 2022

A Diretora da Agência Nacional de Vigilância Sanitária, no uso de suas atribuições e tendo em vista o disposto no art. 203, III, § 3º, aliado ao art.171, V do Regimento Interno aprovado pela Resolução de Diretoria Colegiada - RDC nº 585, de 10 de dezembro de 2021, resolve:

Art. 1º Instituir Grupo de Trabalho na Anvisa para discussão das melhores práticas científicas regulatórias para avaliação de aplicações biofarmacêuticas de modelagem farmacocinética baseada em fisiologia (PBBM).

Art. 2º Compete ao Grupo de Trabalho:

I - Discutir as melhores práticas científicas e regulatórias para avaliação de aplicações biofarmacêuticas de modelagem farmacocinética baseada em fisiologia (PBBM) com base em casos submetidos via projeto de colaboração entre indústrias farmacêuticas associadas ao IQ Consortium (International Consortium Innovation & Quality in Pharmaceutical Development) e agências reguladoras, incluindo ANVISA, Food and Drug Administration (FDA - EUA), Health Canada (Canadá) e The Medicines and Healthcare Products Regulatory Agency (MHRA - Reino Unido).

II - Capacitar os servidores envolvidos a realizar análises técnicas de modelos PBBM submetidos oficialmente à Gerência-Geral de Medicamentos da Anvisa.

III - Propor diretrizes para a submissão de dados e avaliação regulatória de modelos PBBM.

2022-23: focus on cases and training

2023-24: focus on assessment workflows

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3. PBBM REGULATORY SCENARIO, INITIATIVES & PERSPECTIVES IN BRAZIL

- PBBM acceptance for review discussed case by case
  - Early interactions (i.e.: question formulary or meeting request) with CETER or GQMED
  - Data assessment discussed by PBBM WG
- Working on alignment/amendments needed on current ANVISA regulations
  - Related to biopharmaceutics analysis: QbD, CMC/SUPAC changes, dissolution, IVIVC, BE/ BW
  - Related to MIDD policies: need for M&S/ PBPK/ PBBM GL
- Working on actions to multiply and institutionalize discussion
  - Further involvement of other ANVISA offices, local/ generic based industry and academia experts
- Need to have biopharmaceutic risk assessment frameworks and PBBM decision trees
  - For industry and regulator to guide applicability/ need of PBBM
  - For critical PBBM parameters/ steps (e.g.: solubility, precipitation, integration of dissolution)

Acknowledgments:

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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

Any question?

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