Application of PBBM in generic product development

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Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives
29th – 31st Aug, 2023

Dr.Reddy's

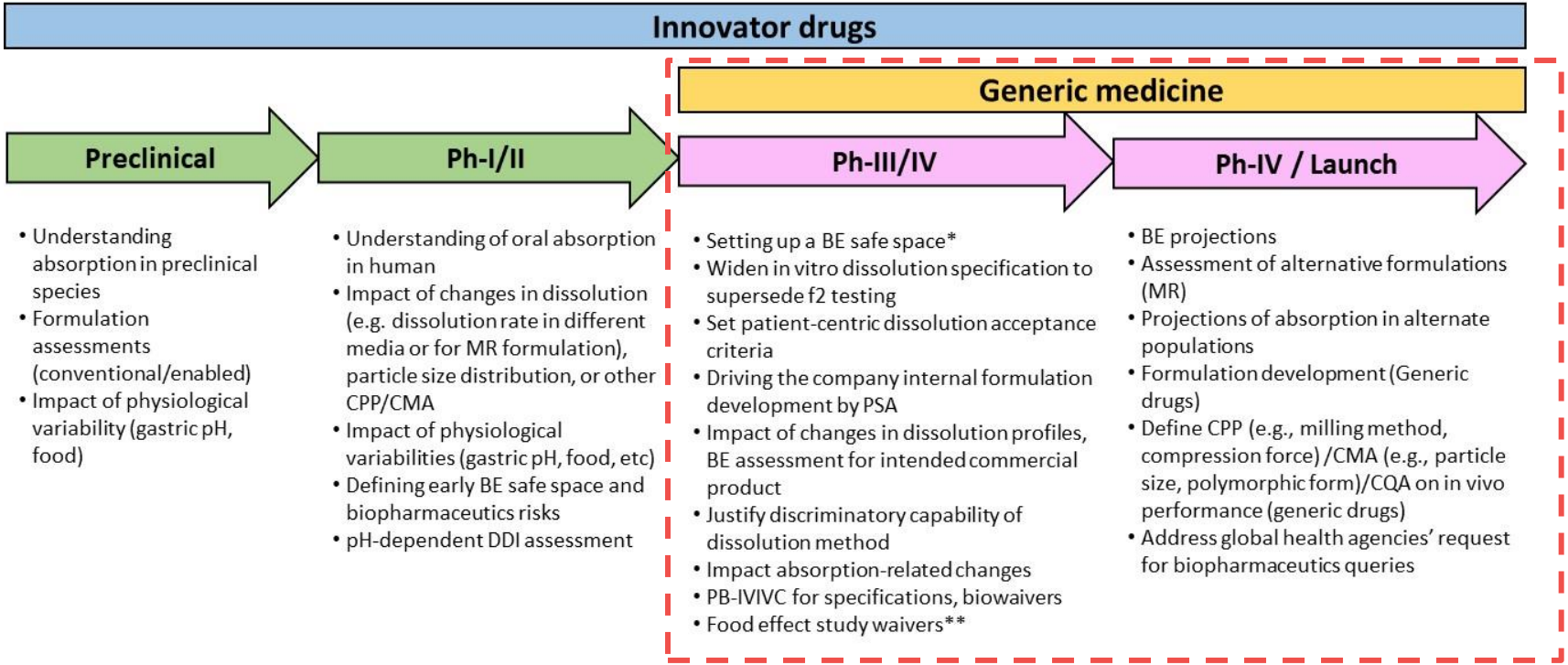
Disclaimer

The opinions expressed herein are solely those of the presenter and do not represent statements or opinions of Dr. Reddy's Laboratories Ltd.

Agenda

- Biopharmaceutics driven generic product development
  - PBPK / PBBM Modeling
- PBBM modeling framework
  - General modeling workflow
  - Dissolution data integration
  - Bio-predictive vs QC dissolution media
- Industry Case studies
  - 1 # Critical Bioavailability Attributes (CBA's) evaluation
  - 2 # Impact of faster dissolution profiles on safety
  - 3 # Gender impact on pharmacokinetics
  - 4 # Discriminatory power of dissolution method (DDDPlus)
- Common regulatory queries received on PBBM modeling
- Conclusions, way forward

Applications of PBBM modeling drug product life cycle

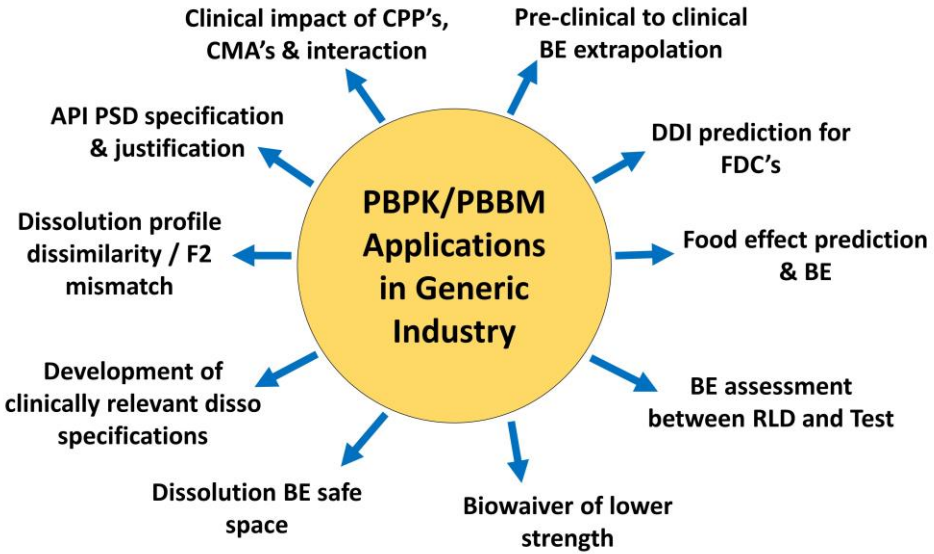


- PBBM modeling in generic product development can be initiated as early as Ph-III/IV or Ph-IV/launch

Di W et al. Physiologically Based Pharmacokinetics Modeling in Biopharmaceutics: Case Studies for Establishing the Bioequivalence Safe Space for Innovator and Generic Drugs, Pharm Res. 2023, https://doi.org/10.1007/s11095-022-03319-6

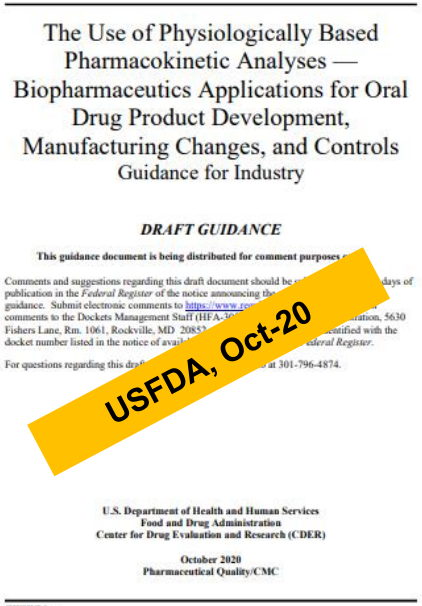
PBBM Modeling in generic product development

- In generic industry, PBBM modeling has various applications from product development to commercialization
- Such modeling based justifications and approaches are accepted by regulatory agencies such as USFDA, EMA in clinico-regulatory justifications
- A validated model can avoid potential clinical study thereby saving cost, time leading to faster development of generic medicines



Yuvaneshwari et al. Applications of PBPK/PBBM modeling in generic product development: An industry perspective. J Drug Del Sci Technol. 2022, https://doi.org/10.1016/j.jddst.2022.103152

PBBM Modeling – Regulatory guidance's



The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes

Comments and suggestions regarding this draft document should be s… days of publication in the *Federal Register* of the notice announcing th… guidance. Submit electronic comments to https://www.reg… comments to the Dockets Management Staff (HFA-30… ration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852… entified with the docket number listed in the notice of avail… *Federal Register*.

For questions regarding this dra… at 301-796-4874.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Pharmaceutical Quality/CMC

USFDA, Oct-20

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

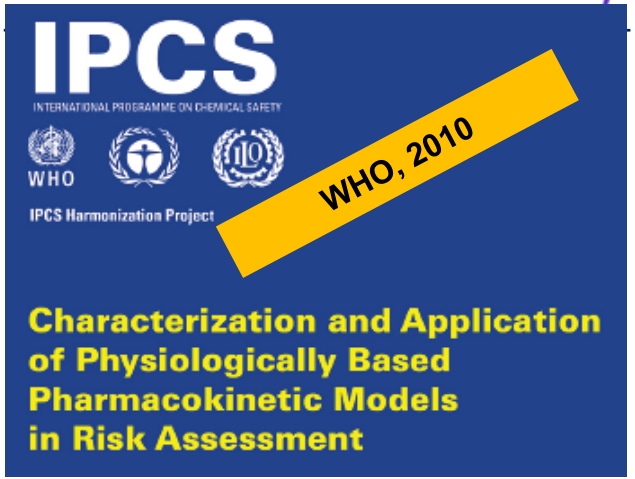
13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

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

Draft agreed by Modelling and Simulation Working G…	April 2016
Draft agreed by Pharmacokinetics Worki…	May 2016
Adopted by CHMP for release fo…	21 July 2016
Start of public consul…	29 July 2016
End of cons… comments)	31 January 2017
Agreed by M… Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	

Keywords	*pharmacokinetics, modelling, simulation, qualification, predi… performance*

EMA, 2018



IPCS
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
WHO
IPCS Harmonization Project

Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

WHO, 2010

J Pharm Sci. 2021 Feb;110(2):594-609. doi: 10.1016/j.xphs.2020.10.059. Epub 2020 Nov 3.

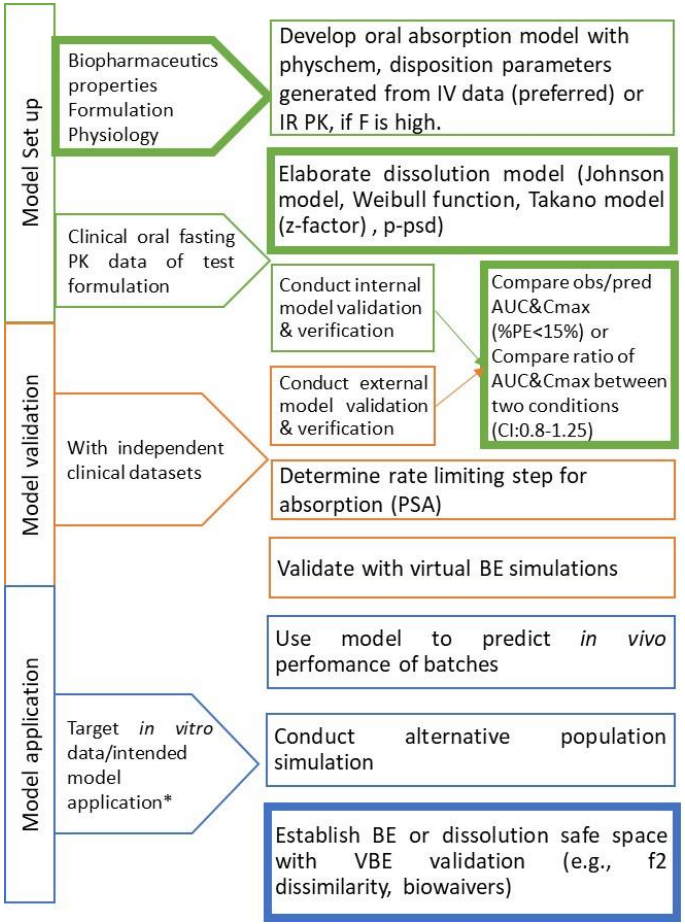
Applications of Physiologically Based Biopharmaceutics Modeling (PBBM) to Support Drug Product Quality: A Workshop Summary Report

13 Office of Advanced Evaluation with Electronic Data, Pharmaceuticals and Medi… Agency (PMDA), Tokyo, Japan.
14 General Office of Medicines and Biological Products, Brazilian He… (Anvisa), Brasilia, Brazil.
15 National Institutes for Food and Drug Control (NIFDC), Beijing…

ANVISA, NIFDC, CHINA; PMDA, 2019

- Apart from USFDA, EMA, other agencies such as ANVISA, MEDSAFE, CDE are also open to PBBM submissions

PBBM model development – general workflow



- ***Literature data, experimental data, ADMET predicted data***
- ***Adequate justification for all input parameters***

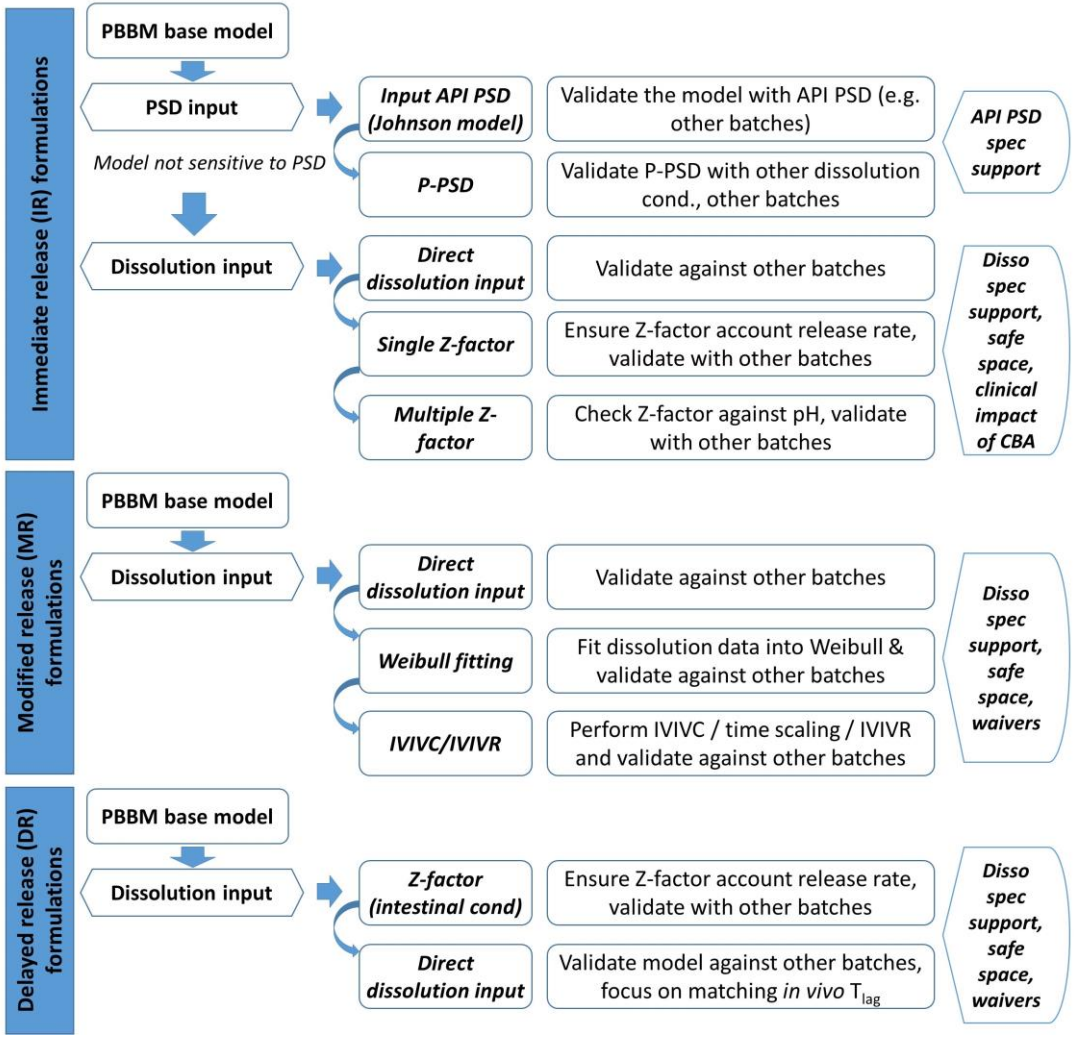
- ***Validation against literature data, in-house data, population bioequivalence and virtual simulations***
- ***Population – representative of clinical study, race, variability***
- ***Validation against multiple studies to ensure model robustness***

- ***Apply model for intended application, conduct virtual BE simulations***
- ***Derive conclusions from physiological perspective***

Di W et al. Physiologically Based Pharmacokinetics Modeling in Biopharmaceutics: Case Studies for Establishing the Bioequivalence Safe Space for Innovator and Generic Drugs, Pharm Res. 2023, https://doi.org/10.1007/s11095-022-03319-6

Dissolution data integration

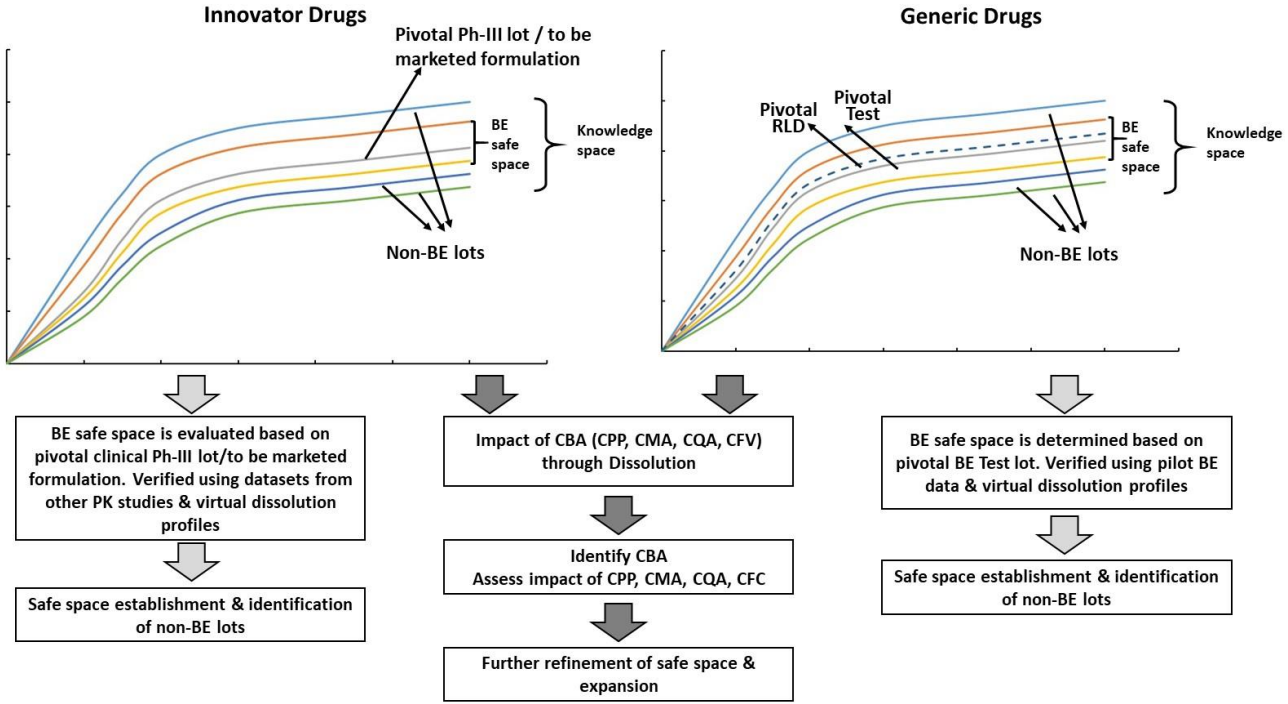
- Dissolution is critical input into PBBM models as it governs in vivo exposure
- Multiple models are available for IR, MR and DR formulations
  - **IR:** API PSD, direct dissolution input, z-factors
  - **MR:** direct dissolution input, Weibull function, IVIVC/IVIVR
  - **DR:** z-factor, direct dissolution input



Kollipara et al. Best Practices for Integration of Dissolution Data into Physiologically Based Biopharmaceutics Models (PBBM): A Biopharmaceutics Modeling Scientist Perspective. AAPS PharmSciTech, 2023, https://doi.org/10.1208/s12249-023-02521-y

Dissolution safe space

- Dissolution / BE safe space is based on pivotal test BE lot and can further be verified using other clinical studies data and helps to identify non-BE batches



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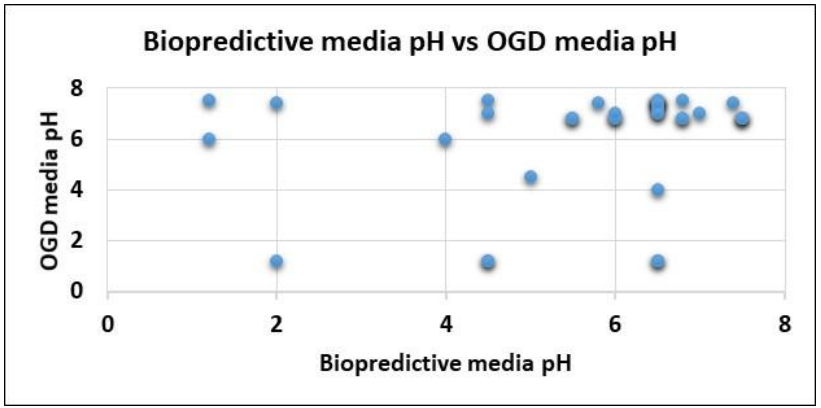
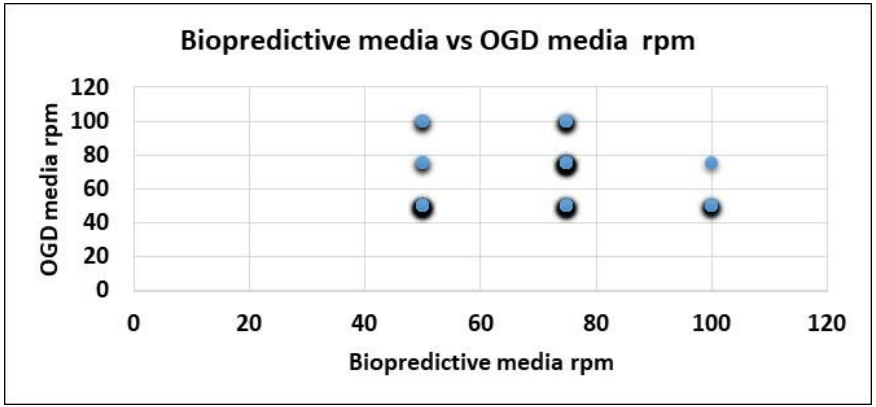
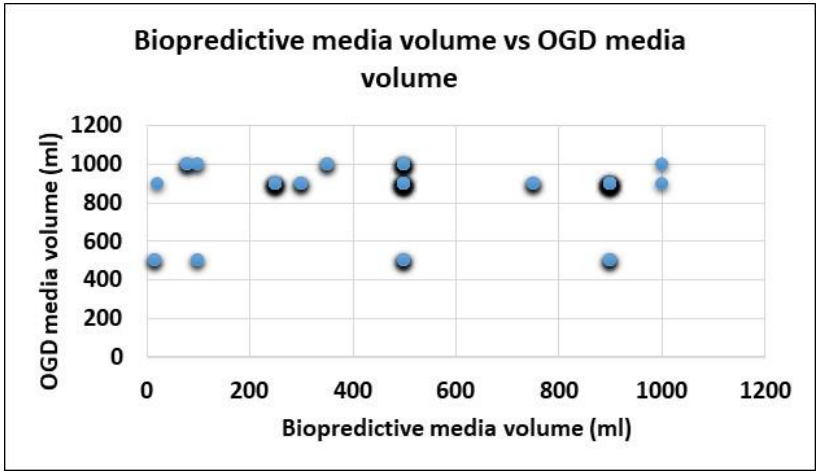
OGD (QC) Vs biopredictive Media





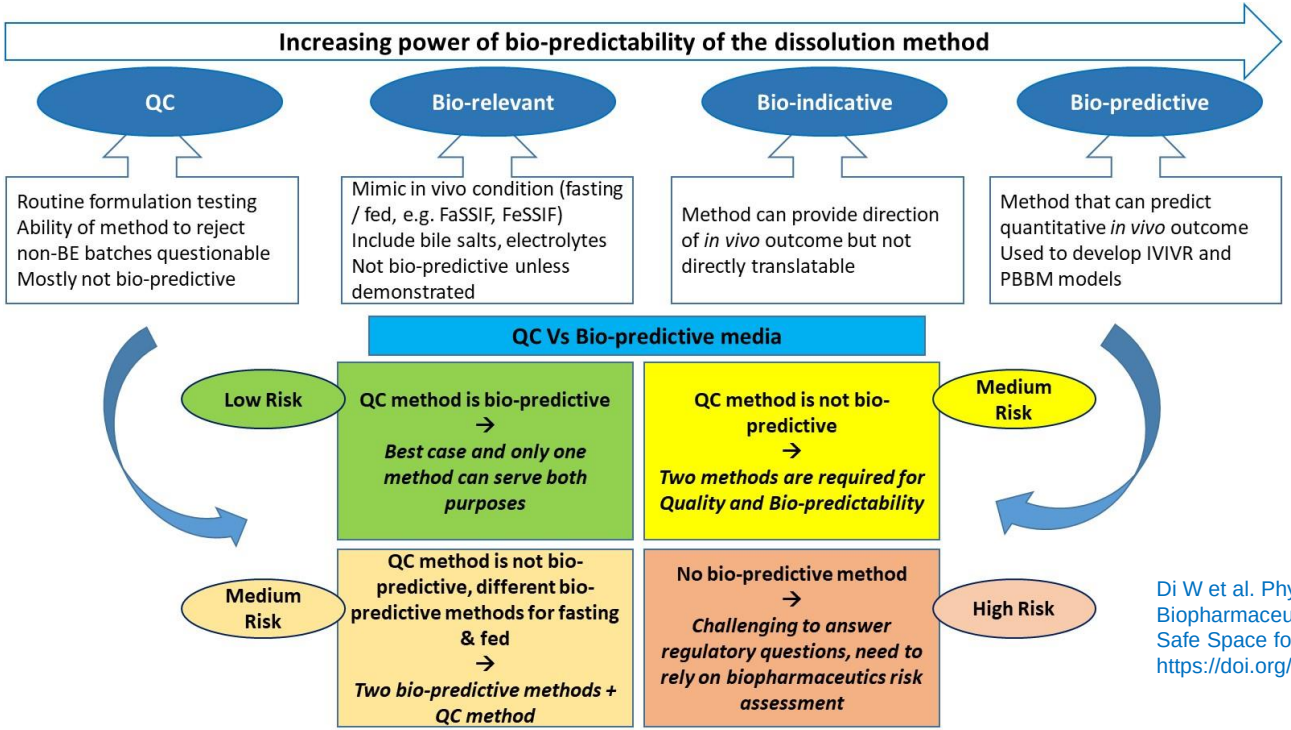


- There are distinct differences with respect to pH, rpm and media volume of biopredictive media's as compared to OGD media
- Typically higher pH, higher volumes and rpm are used in OGD media's whereas lower pH, volume and rpm are used in biopredictive media for discriminatory purpose
- Hence OGD media may not always be of bio-predictive and a separate method is required

Ahmed et al. Biopharmaceutics Risk Assessment—Connecting Critical Bioavailability Attributes with In Vitro, In Vivo Properties and Physiologically Based Biopharmaceutics Modeling to Enable Generic Regulatory Submissions. AAPS J. 2023, https://doi.org/10.1208/s12248-023-00837-y

QC Vs Bio-predictive dissolution media

- All regulatory queries or justifications are based on QC media, however it may not be bio-predictive
- Along with QC media, separate bio-predictive media can help to imbed quality into product development – from manufacturability and clinical perspectives



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Case studies

Case study#1: Critical Bioavailability Attributes (CBA) evaluation

CBA is a formulation or a process variable that is expected to critically impact the bioavailability of a drug product and can be product CMA, CFV or CPP

The AAPS Journal (2023) 25:77
https://doi.org/10.1208/s12248-023-00837-y

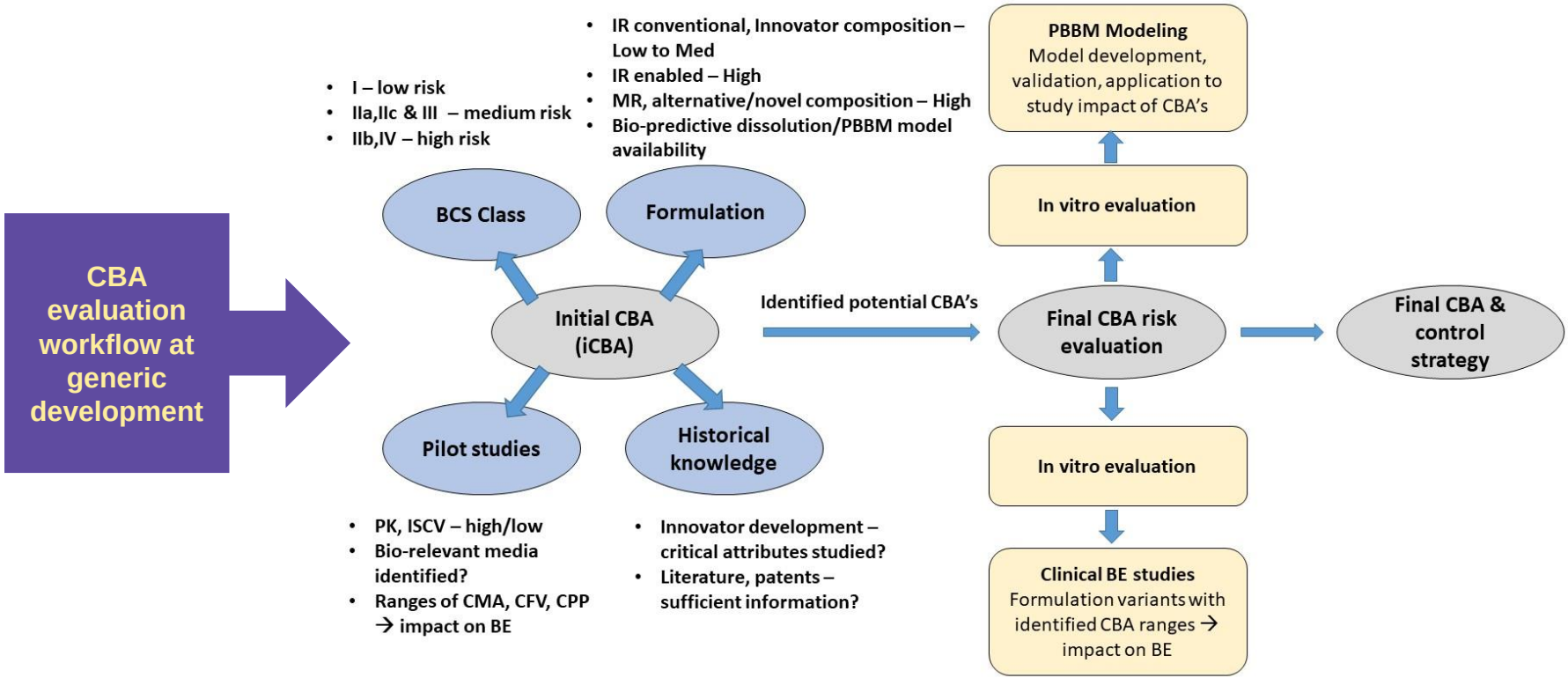
REVIEW ARTICLE

Check for updates

Biopharmaceutics Risk Assessment—Connecting Critical Bioavailability Attributes with *In Vitro, In Vivo* Properties and Physiologically Based Biopharmaceutics Modeling to Enable Generic Regulatory Submissions

Tausif Ahmed[1] · Sivacharan Kollipara[1] · Rajkumar Boddu[1] · Adithya Karthik Bhattiprolu[1]

Case study#1: Critical Bioavailability Attributes (CBA) evaluation



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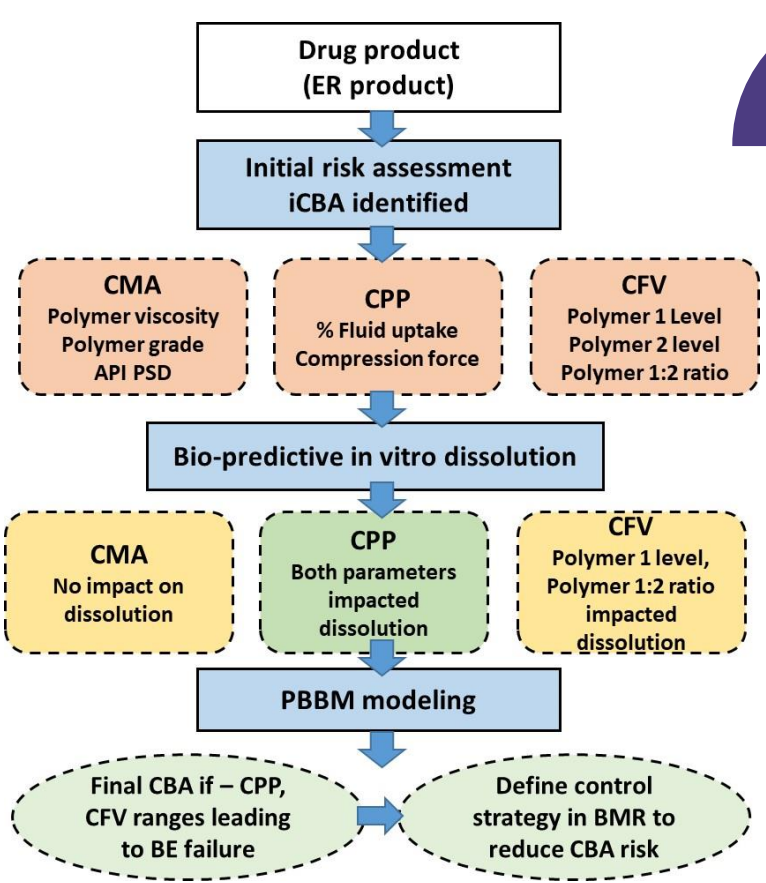

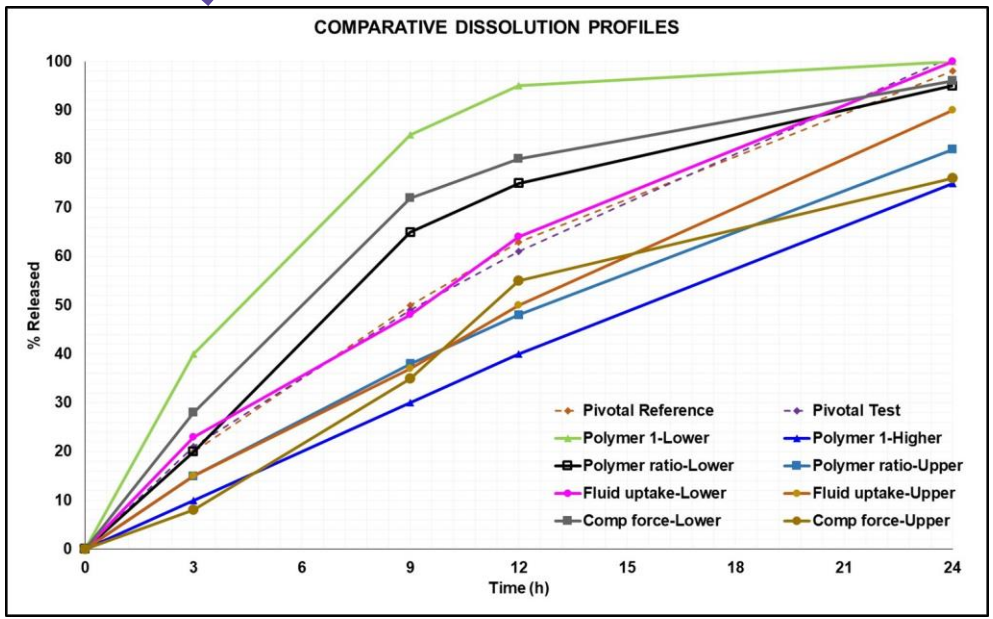

Ahmed et al. Biopharmaceutics Risk Assessment—Connecting Critical Bioavailability Attributes with In Vitro, In Vivo Properties and Physiologically Based Biopharmaceutics Modeling to Enable Generic Regulatory Submissions. AAPS J. 2023, https://doi.org/10.1208/s12248-023-00837-y

Case study#1: Critical Bioavailability Attributes (CBA) evaluation

Comparison	CBA	C_{max} T/R, 90% CI	AUC_{inf} T/R, 90% CI
Model Validation	Pivotal Test vs Pivotal RLD	97.91 (93.28-102.77) [104.4 (96.95-112.43)]*	98.29 (91.27-105.86) [99.81 (91.97-108.32)]*
Pivotal Test	Low level polymer 1	125.4 (119.27-131.82)	111.9 (104.23-120.1)
	High level polymer 1	80.22 (75.78-84.93)	83.57 (77.09-90.6)
	High Polymer 1:2 ratio	83.69 (79.33-88.29)	88.18 (81.56-95.33)
	Low Polymer 1:2 ratio	108.4 (103.09-113.89)	103 (95.79-110.77)
	Low fluid uptake	110.2 (104.83-115.9)	104.7 (97.42-112.45)
	High fluid uptake	95.85 (91.28-100.66)	99.02 (91.75-106.87)
	Low compression force	111.6 (106.09-117.46)	107.1 (99.47-115.24)
	High compression force	89.53 (84.84-94.49)	83.18 (77.05-89.79)
Pivotal RLD	Low level polymer 1	122.8 (117.54-128.23)	110 (102.8-117.66)
	High level polymer 1	78.55 (74.61-82.69)	82.14 (75.99-88.79)
	High Polymer 1:2 ratio	81.94 (78.14-85.93)	86.67 (80.41-93.42)
	Low Polymer 1:2 ratio	106.1 (101.59-110.79)	101.2 (94.46-108.53)
	Low fluid uptake	107.9 (103.3-112.74)	102.9 (96.07-110.17)
	High fluid uptake	93.85 (89.97-97.90)	97.33 (90.46-104.72)
	Low compression force	109.3 (104.54-114.27)	105.2 (98.09-112.91)
	High compression force	87.66 (83.56-91.96)	81.76 (75.97-87.98)

Ahmed et al. Biopharmaceutics Risk Assessment—Connecting Critical Bioavailability Attributes with In Vitro, In Vivo Properties and Physiologically Based Biopharmaceutics Modeling to Enable Generic Regulatory Submissions. AAPS J. 2023, https://doi.org/10.1208/s12248-023-00837-y

Case study#1: Critical Bioavailability Attributes (CBA) evaluation

Final CBA Risk assessment

CBA	Probability (happened in the past)	Severity (Impact on in vitro / in vivo performance)		Detectability (Disso or PBBM)		Final CBA assessment	Can it be controlled?	Control Strategy?
	Score	Score	Impact	Score	Detection			
Polymer 1 viscosity	Low	Low	NA	High	NA	Low	Yes	Specification
Polymer 1 grade	Low	Low	NA	High	NA	Low	Yes	Specification
API PSD	Low	Low	NA	High	Dissolution	Low	Yes	Specification
Polymer 1 level	Low	High	*In vitro & In vivo* (PBBM)	High	Dissolution, PBBM	Low	Yes	BMR
Polymer 2 level	Low	Medium	NA	High	Dissolution	Low	Yes	BMR
Polymer 1:2 ratio	Low	High	*In vitro & In vivo* (PBBM)	High	Dissolution, PBBM	Low	Yes	BMR
% Fluid uptake	Low	High	*In vitro & In vivo* (PBBM)	High	Dissolution, PBBM	Low	Yes	BMR
Compression force	Low	High	*In vitro & In vivo* (PBBM)	High	Dissolution, PBBM	Low	Yes	BMR

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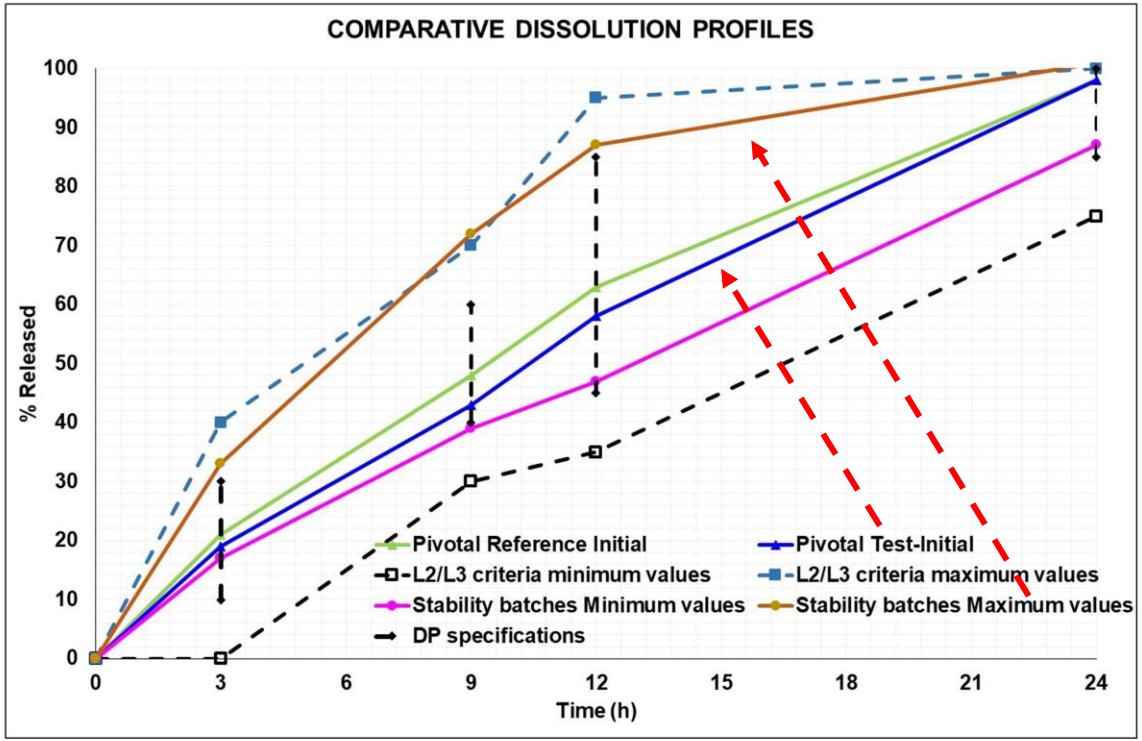
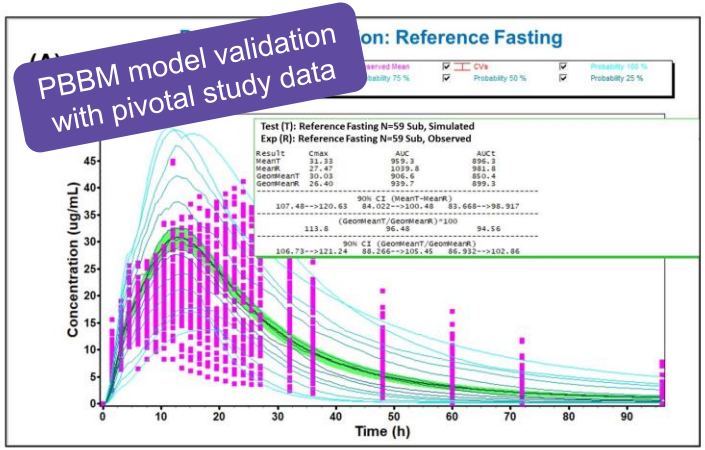
Case study#2: Impact of faster dissolution profiles on safety of NTI product

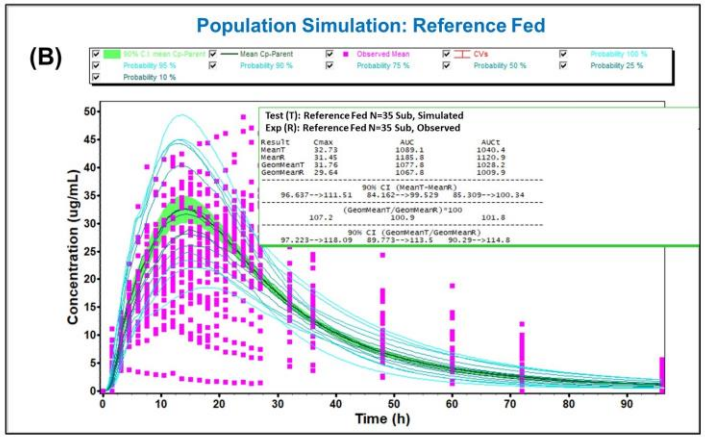
- Product is an extended release formulation containing an anti-epeliptic NTI drug
- Product exhibited faster dissolution profiles during stability
- Agency asked to evaluate impact of faster dissolution profiles on safety
- Along with stability profiles, impact on extreme boundaries of dissolution (i.e. at specification levels) were also evaluated



Case study#2: Impact of faster dissolution profiles on safety of NTI product

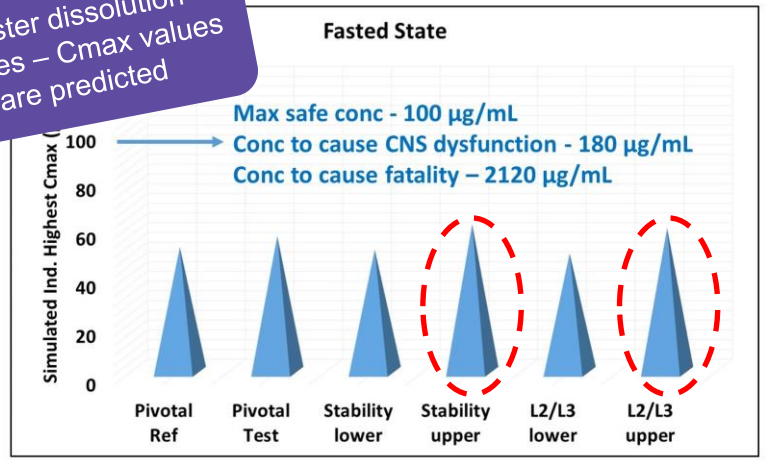
PBBM model validation with pivotal study data

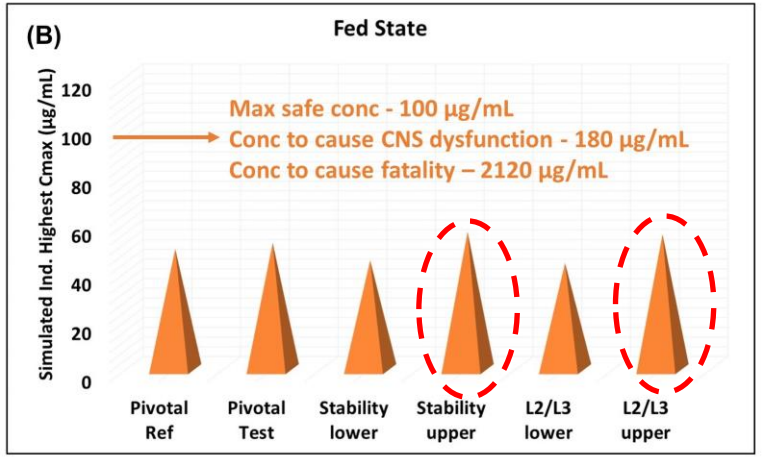




Predicted C_{max} in all cases are less than reported safety limits, hence no safety concerns with product

Faster dissolution profiles – Cmax values are predicted



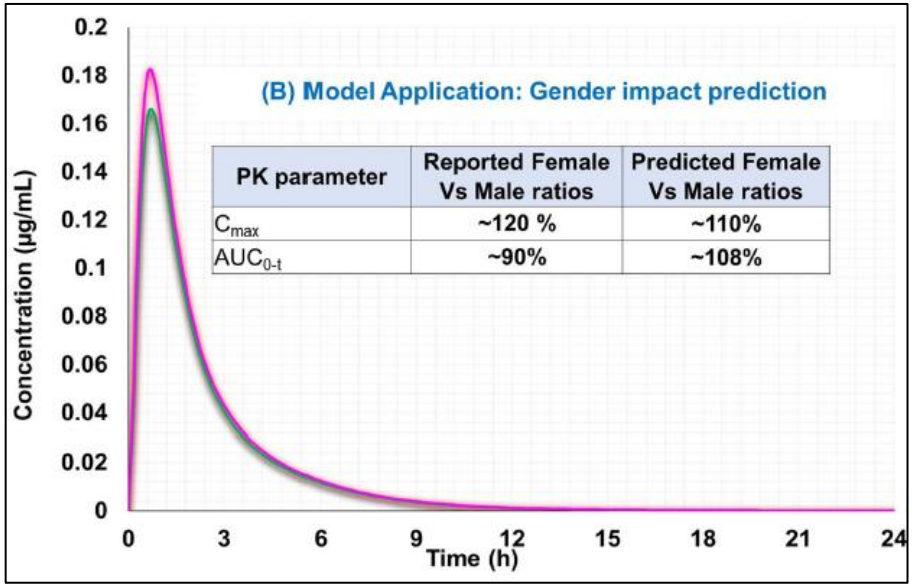


Case study#3: Gender impact evaluation with PBPK modeling

- For IR product containing BCS Class II molecule, the following regulatory query has been received:

- Only males were included in fasting and fed bioequivalence studies. As product is intended for both sexes, provide a scientific justification that BE results in male can be extrapolated to entire population consisting of both sexes.

- Socio-cultural reasons in India, it may not be possible to include equal number of female subjects in BE studies
- PBPK model was utilized to assess impact of gender on pharmacokinetics of the product
- Enzyme, transporter kinetics were incorporated and thorough validation has been performed against pivotal study
- Further, exposures in females were predicted and compared against male population



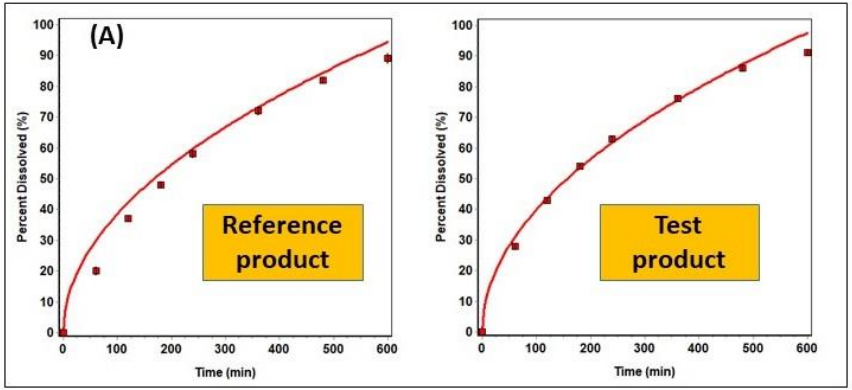
PK parameter	Reported Female Vs Male ratios	Predicted Female Vs Male ratios
C_{max}	~120 %	~110%
AUC_{0-t}	~90%	~108%

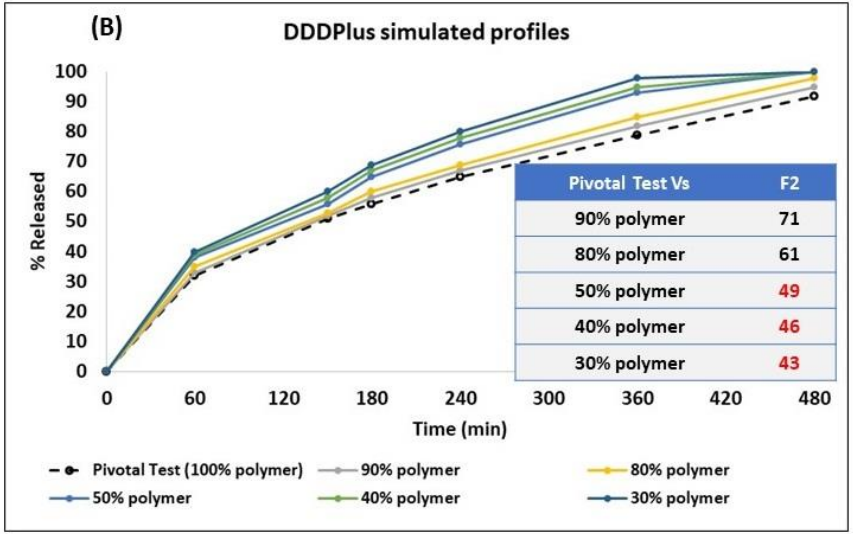
The model predicted female/male exposures inline with literature, justified absence of impact of gender on bioequivalence

Boddu et al. Power of integrating PBPK with PBBM (PBPK-BM): a single model predicting food effect, gender impact, drug-drug interactions and bioequivalence in fasting & fed conditions. Xenobiotica. 2023. https://doi.org/10.1080/00498254.2023.2238048

Case study#4: Discriminatory power of dissolution method with DDDPlus

- Drug product contains BCS III API at drug load of 60%
- No discrimination has been observed in QC media and hence agency asked to justify discriminatory power of dissolution method
- Due to high solubility nature of API and high drug load, it was not possible to demonstrate discrimination
- Practically it was not possible to manufacture batches with significantly lower or higher polymer
- DDDPlus was used to demonstrate discrimination / f2 failure and edge of failures have been identified
- Concluded that media is discriminatory but because of high soluble nature and high drug load, discrimination is not clearly evident





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Common regulatory queries on PBBM justifications

Query / concern	Probable solution
Justification / optimization performed for model inputs (e.g. Peff)	Experimental or literature support for model parameters PSA to demonstrate optimized value, details about optimization algorithm used
Z-factor for dissolution data input	Inherent issues of z-factor, demonstrate calculation method – solubility, time points, fit. Demonstrate z-factor in relation to absorption dissolution curves
Dissolution method: bio-relevance (QC), ability to reject non-BE batches	Develop parallel bio-predictive media, may be difficult for IR formulations Pilot BE data (e.g. failed) helps to show method relevancy
Mechanistic framework of model (e.g. ADME process)	PBPK can be adapted, mass-balance diagram in justification can help Demonstrating first pass effect, model's ability to capture bioavailability
Consideration of CBA's (e.g. CPP, CMA, CQA, CFV) in the model	Follow CBA evaluation workflow, include product quality attributes in the model and provide justification
Validation against failed BE data	Validation against pilot BE data, especially failed BE
Totality of evidence	Include biopharmaceutics risk assessment along with PBBM as appropriate
Different release rates and corresponding IVIVC	Ideal to have BE against different polymers and release rates
Discriminatory power of the QC media	Use DDDPlus to identify excipient ranges that can result in f2 mismatch (works in cases where dissolution method is not sensitive to formulation changes)
Gender impact in BE studies	Performing modeling with male, female physiologies and correlation with literature

Conclusions

- PBBM modeling has demonstrated applications in both generic and innovator domain
- Apart from USFDA and EMA, other agencies such as ANVISA, MEDSAFE, CDE open to modeling based justifications
- For generics, PBBM modeling has clearly demonstrated its value to avoid BE studies in cases of dissolution specifications justification, f2 mismatch, lower strength biowaivers etc
- Focus areas of PBBM modeling:
    - Bio-predictive ability of QC media
    - Regulatory justifications: mechanistic frame work, ability to predict failed BE data, dissolution method discriminatory power
    - Upcoming areas: waiver of fed studies and multiple dose steady state studies
- CBA's evaluation framework can be utilized by generic companies to facilitate regulatory submissions. PBBM modeling also can enable CBA's evaluation through creation of safe space
- Overall, PBBM modeling is increasingly being recognized, regulatory agencies are open to such submissions, knowledge sharing mainly in terms of regulatory justifications is required across academia, industry and agency

Acknowledgements

- Dr. Tausif Ahmed and Biopharmaceutics team at Global Clinical Management (GCM) group at DRL
- Dr. Reddy's Management for providing all infrastructure and support
- All other CFTs, collaborators and Regulator's who have contributed to the data generation/feedback for these case studies
- Organizing committee for giving me this opportunity

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Thank You