Application of PBBM Modeling in Generic Product Development: Regulatory Applications and Case Studies

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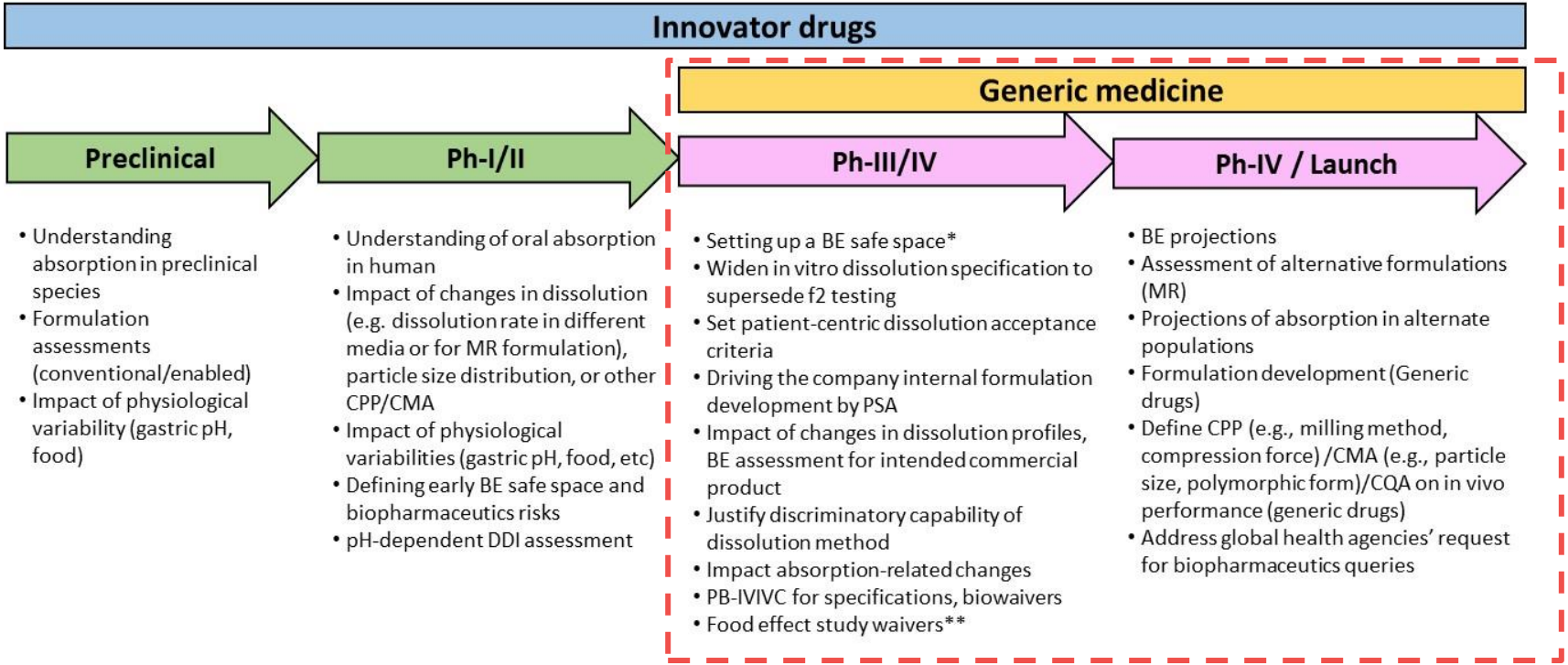
Disclaimer

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

Agenda

- PBBM modeling in generic product development
- PBBM model development
  - General modeling workflow
  - Dissolution data integration
  - Bio-predictive vs QC dissolution media
- Case studies
  - Biowaiver of lower strength due to f2 mismatch
  - Biowaiver for BE leverage
  - Dissolution specification justification
- Common regulatory queries on PBBM justifications
- Conclusions, way forward

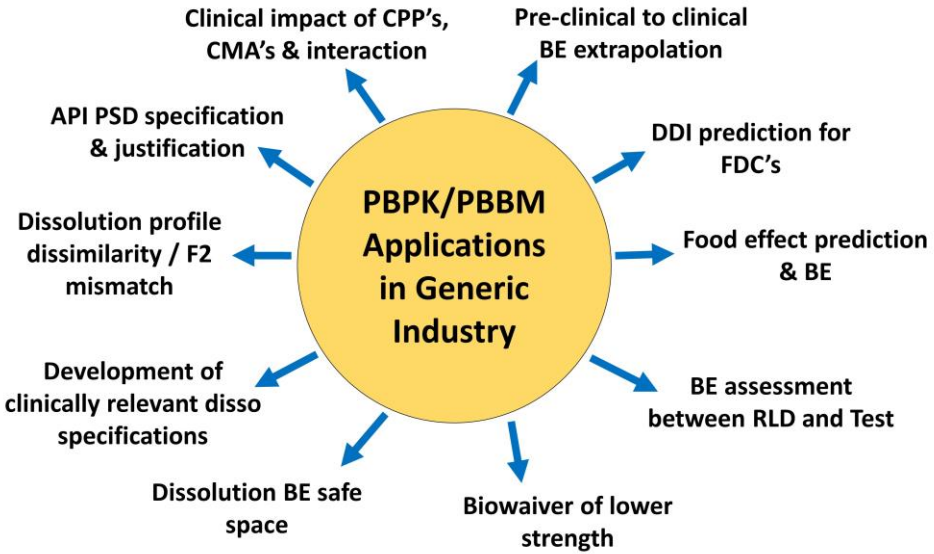
Applications of PBBM modeling drug product life cycle



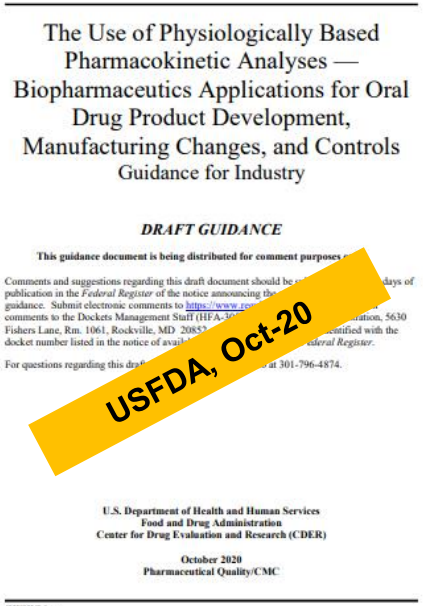
- PBBM modeling in generic product development can be initiated as early as Ph-III/IV or Ph-IV/launch

PBBM Modeling in generic product development

- PBBM / PBPK modeling is a tool that can combine API, formulation, pharmacokinetics with physiology to enable prediction of in vivo exposures (i.e. plasma conc. time profiles) in fasting & fed conditions
- In generic industry, PBBM modeling has various applications from product development to commercialization
- Such 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



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DRAFT GUIDANCE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

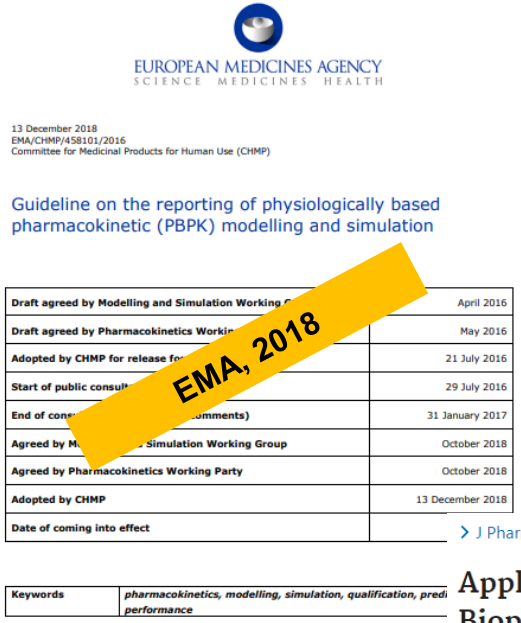
Comments and suggestions regarding this draft document should be ... days of publication in the *Federal Register* of the notice announcing the ... guidance. Submit electronic comments to https://www.regu... comments to the Dockets Management Staff (HFA-305), ...ration, 5630 Fishers Lane, Rm. 1061, Rockville, 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

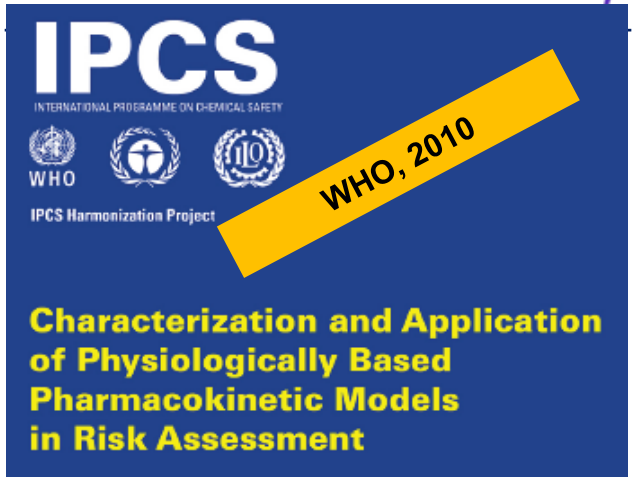
13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

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



WHO, 2010

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

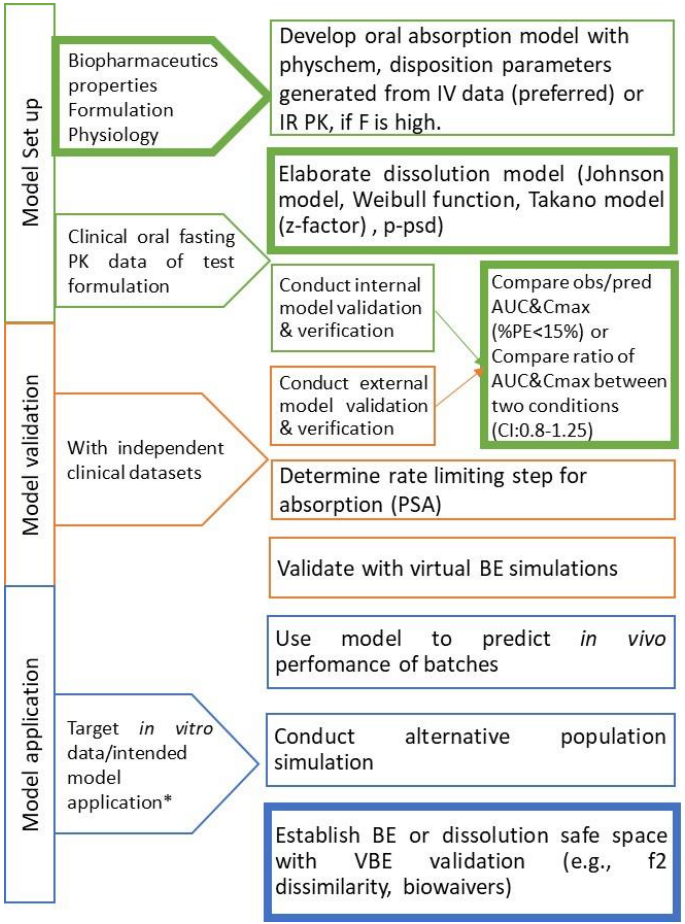
Applications of Physiologically Based Biopharmaceutics Modeling (PBBM) to Support Drug Product Quality: A Workshop Summary Report

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



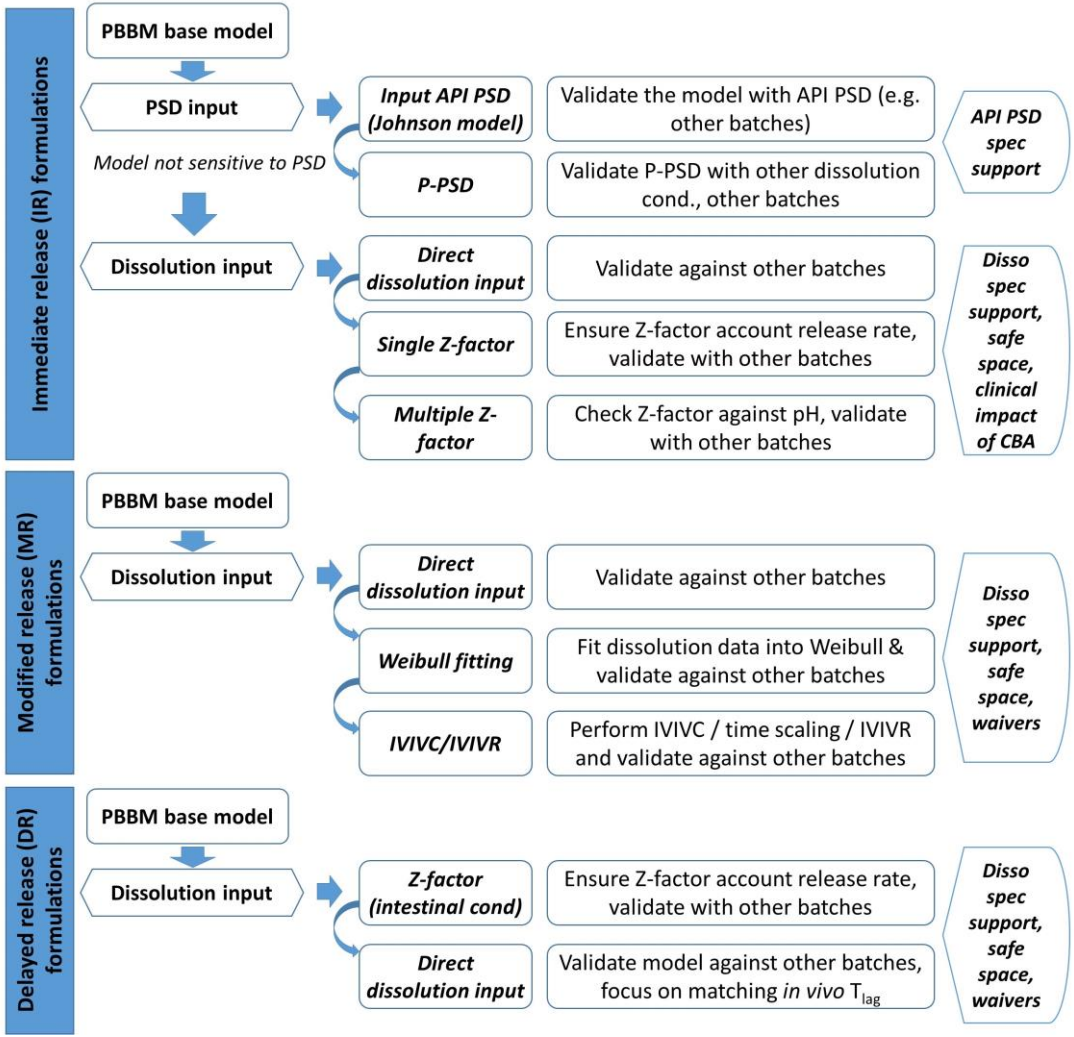
- ***Literature data, experimental data, ADMET predicted data***
- ***Adequate justification for all input parameters***

- ***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***

Dissolution data integration

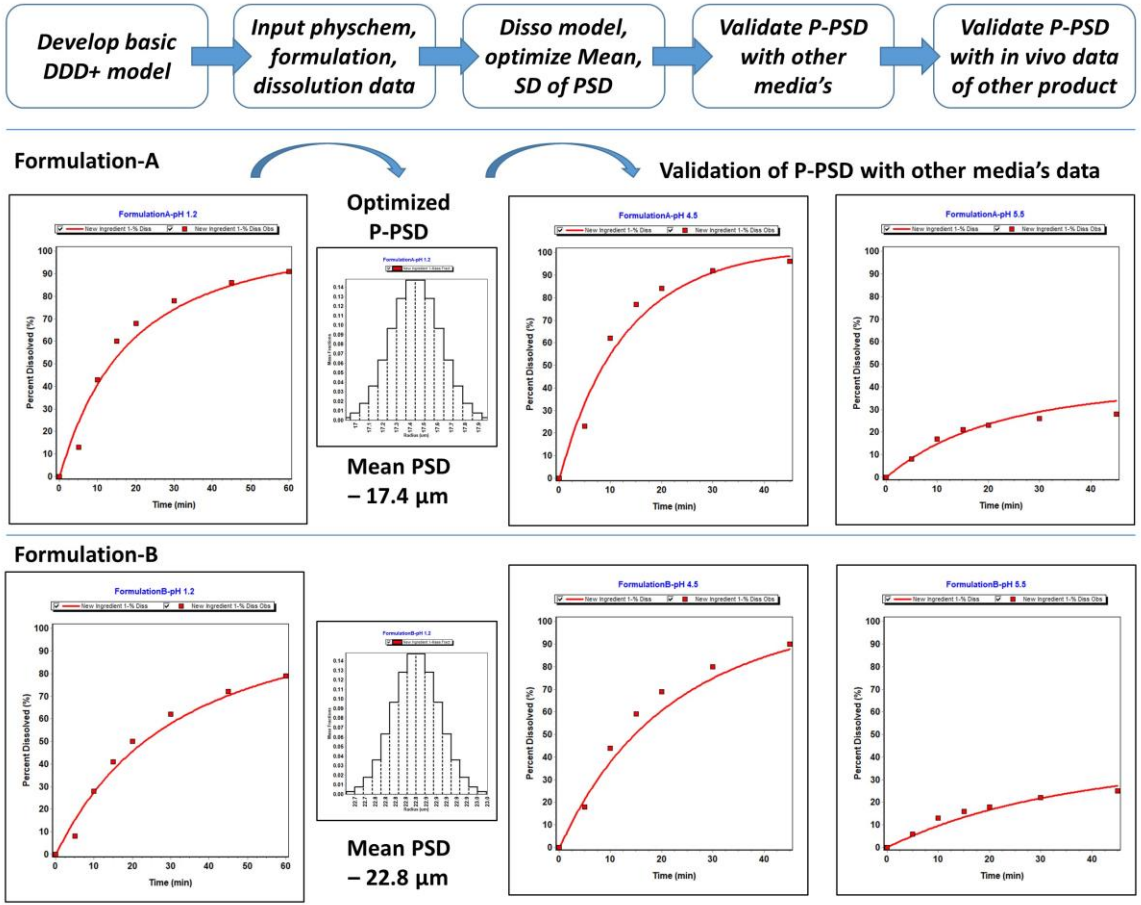
- Dissolution is critical input into PBBM models as it governs in vivo exposure
- Multiple models are available for IR, MR and DR formulations
  - **IR:** API PSD, direct dissolution input, z-factors
  - **MR:** direct dissolution input, Weibull function, IVIVC/IVIVR
  - **DR:** z-factor, direct dissolution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



Ref: Best Practices for Integration of Dissolution Data into Physiologically Based Biopharmaceutics Models (PBBM): A Biopharmaceutics Modeling Scientist Perspective.
Sivacharan Kollipara, Adithya Karthik Bhattiprolu, Rajkumar Boddu, **Tausif Ahmed**, Siddharth Chachad; **AAPS PharmSciTech (2023) 24:59**

P-PSD model using DDDPlus

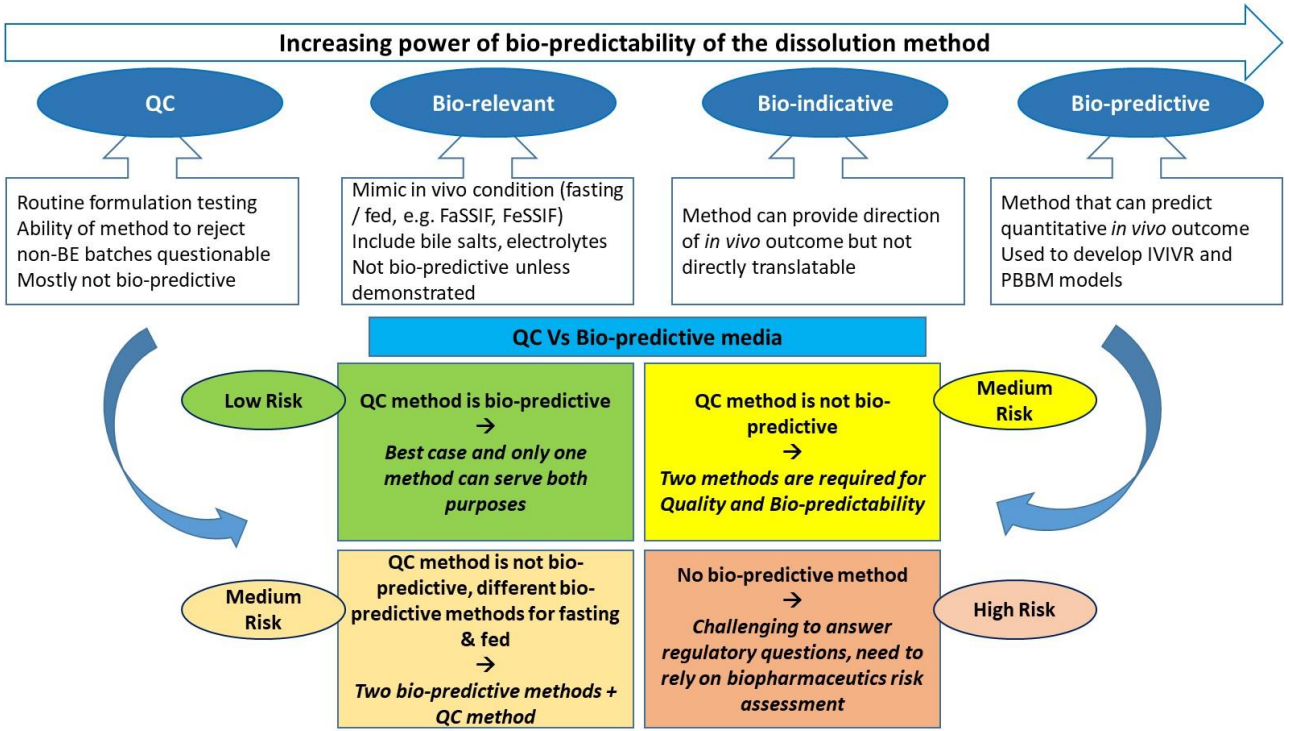
- P-PSD determines effective API PSD in the formulation
- It can be transferred to Gastroplus without having need of additional dissolution input
- P-PSD to be further validated with additional media's and formulation variants



Ref: Best Practices for Integration of Dissolution Data into Physiologically Based Biopharmaceutics Models (PBBM): A Biopharmaceutics Modeling Scientist Perspective. Sivacharan Kollipara, Adithya Karthik Bhattiprolu, Rajkumar Boddu,
Tausif Ahmed, Siddharth Chachad; **AAPS PharmSciTech (2023) 24:59**

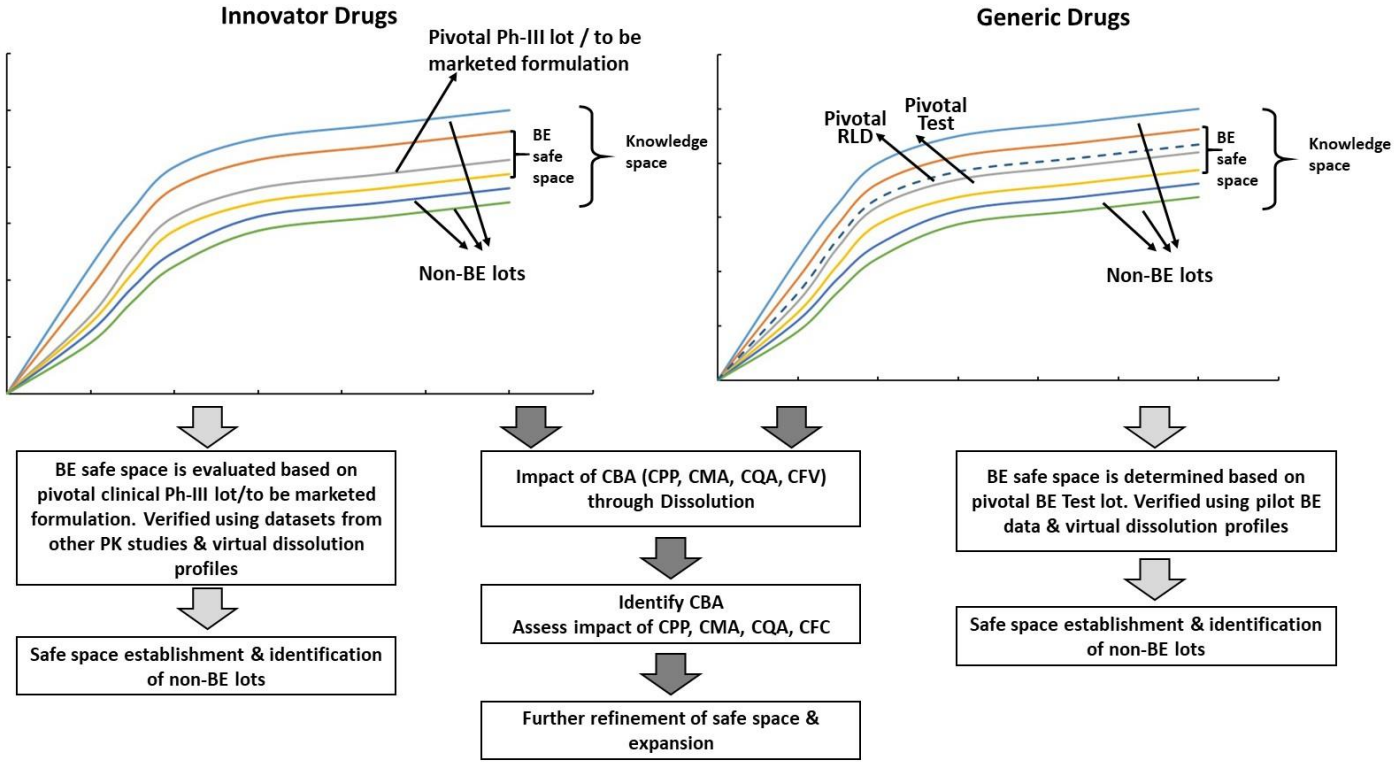
QC Vs Bio-predictive dissolution media

- 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



Dissolution safe space

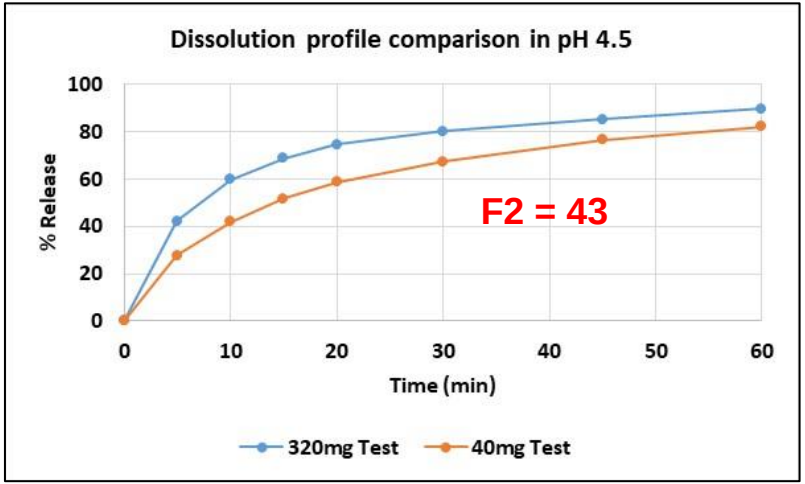
- Dissolution / BE safe space is based on pivotal test BE lot and can further be verified using other clinical studies data and helps to identify non-BE batches



Case studies

Case study#1: Bio-waiver of lower strength in case of f2 mismatch

- Weakly acidic BCS III compound available in 5 strengths: 40, 80, 120, 160, 320mg
- Solubility low in acidic and increases significantly in basic condition
- Crossover fasting BE study conducted on higher strength and BE achieved at 320mg
- In order to obtain bio-waiver for lower strengths, dissolution in multimedia (pH 1.2, 4.5 and 6.8) is required as per EMA guidance
- All combinations met f2>50, except for 40mg in pH 4.5 (f2=43)
- Agency asked to conduct BE study for 40mg strength



PBBM modeling was used to support waiver of 40mg study: faster dissolution profile of 40mg used for 320mg simulations using pH vs z-factor

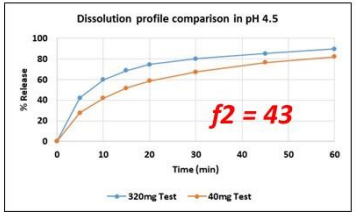
Case study#1: Biowaiver of lower strength in case of f2 mismatch

Model development → API Physicochemical, biopharmaceutical properties
Dissolution data (z-factor vs pH, pH 1.2, 4.5 & 6.8)

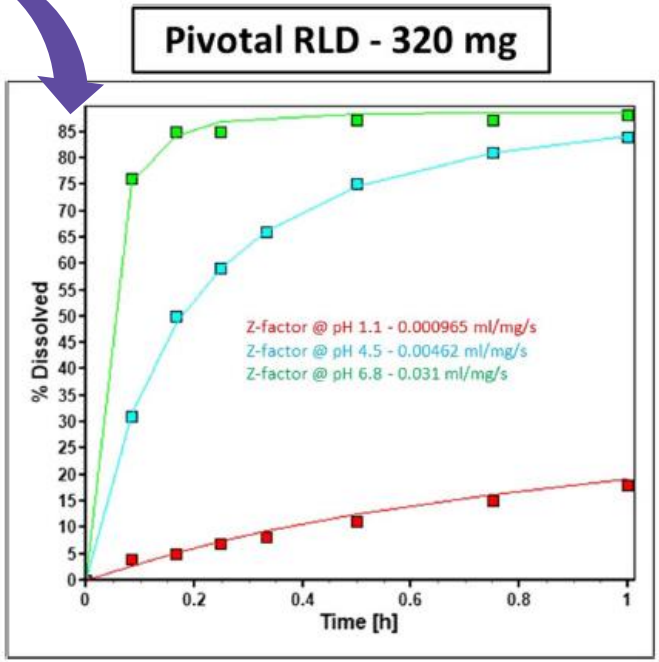
Model validation → Validation using pivotal BE study data in fasting condition, Use of virtual BE simulations

Model application → Validated model used to evaluate in vivo impact of failing f2, by incorporating 40mg dissolution data into 320mg model

Model outcome →



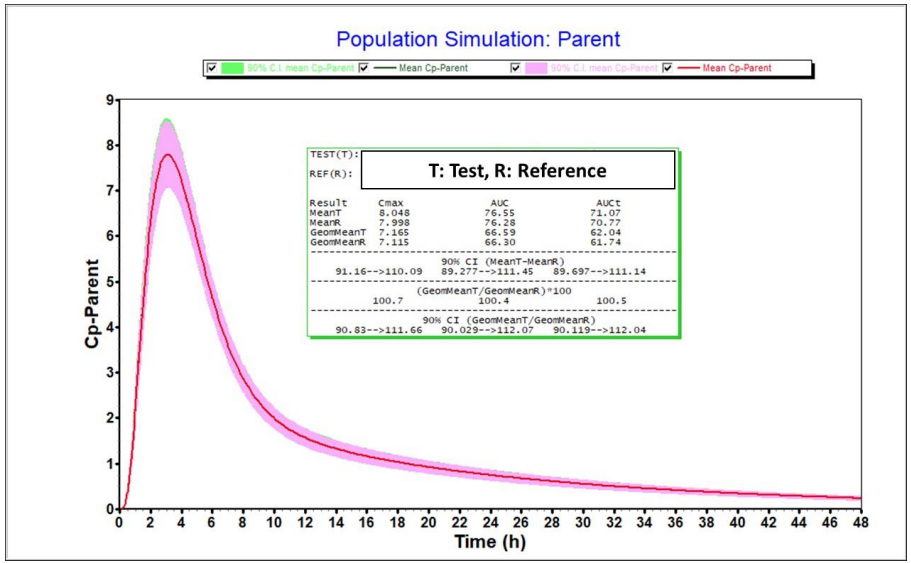
→ *No impact on in vivo, PBBM superseded f2 criteria*



No impact of failing f2 on BE, biowaiver for 40mg was granted

Case study#1: Biowaiver of lower strength in case of f2 mismatch

Pivotal 320mg study BE validation
With Z-factor vs pH input



Cost, time savings, early launch

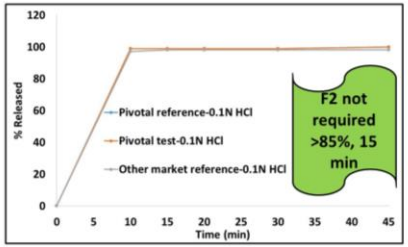
Pivotal 320mg study BE validation

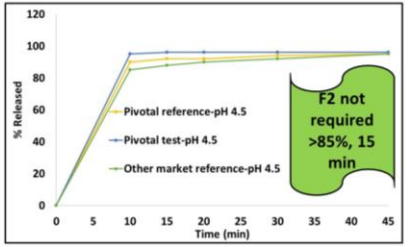
40mg disso against	C_{max}	AUC_{0-t}	AUC_{0-inf}
	T/R (90% CI)		
320mg pivotal Test	99.36 (89.65-110.12)	99.44 (89.13-110.95)	99.40 (89.14-110.83)
320mg pivotal RLD	100.1 (90.27-110.91)	99.88 (89.53-111.44)	99.88 (89.58-111.37)

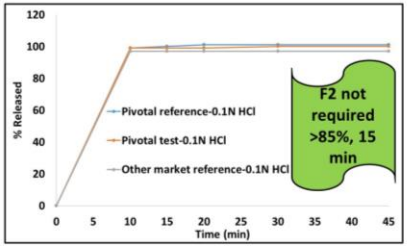
No impact of failing f2 on BE, biowaiver for 40mg was granted

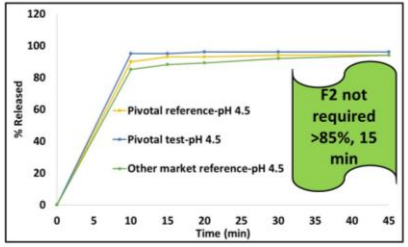
Case study#2: Biowaiver for study leverage, f2 failure

- BCS Class III API, formulation available in two strengths 50mg and 100mg
- Reference & test have two salts, but with same solubility
- BE fasting study was conducted on 100mg in Market-A and while leveraging product to Market-B, reference product of Market-B demonstrated f2<50 in pH 6.8 against pivotal test for both 100mg and 50mg
- Agency denied biowaiver of both strengths 50mg and 100mg due to which BE study was warranted

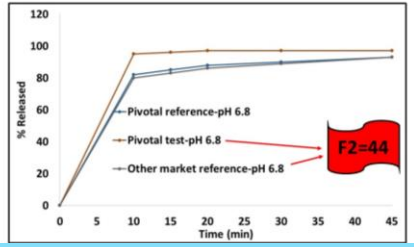




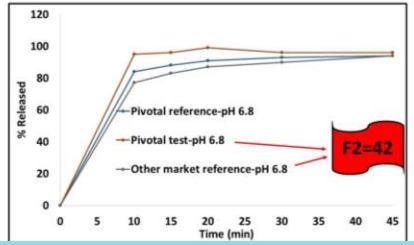




100mg



50mg



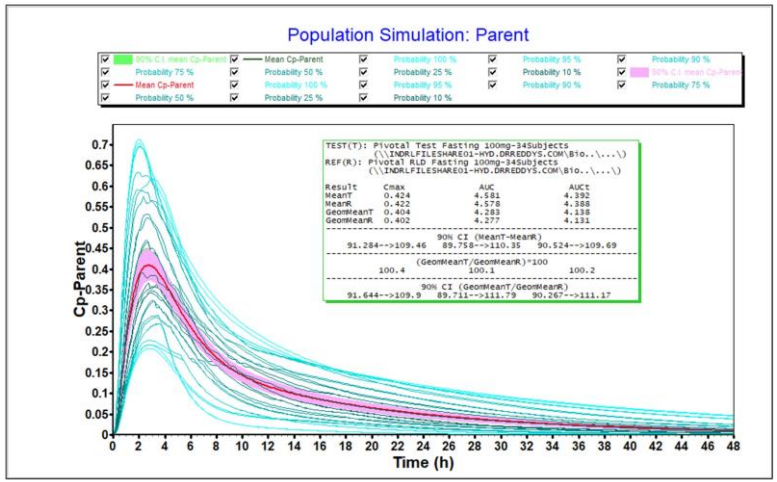
PBBM modeling was used to support waiver of BE study for both 50mg and 100mg

Way forward for BCS biowaiver was proposed → to enable more candidates for waiver

Case study#2: Biowaiver for study leverage, f2 failure

Pivotal 100mg study validation

Z-factor vs pH input



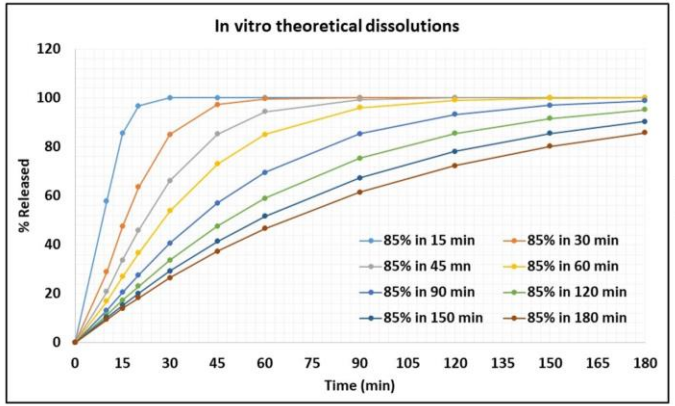
PK parameter	Predicted values	
	Geometric mean ratio	90% confidence intervals
	100mg	
Pivotal Ref vs Pivotal Test		
C_{max} (ng/mL)	100.4 [104.36] *	91.64-109.90 [97.63-111.56] *
AUC_{0-inf} (ng.h/mL)	100.1 [100.66] *	89.711-111.79 [98.39-102.98] *
Pivotal Ref vs Market-B Ref		
C_{max} (ng/mL)	99.0	90.30-108.54
AUC_{0-inf} (ng.h/mL)	99.0	88.78-110.40
Market-B Ref vs Pivotal Test		
C_{max} (ng/mL)	101.4	92.46-111.14
AUC_{0-inf} (ng.h/mL)	101.2	90.71-112.4

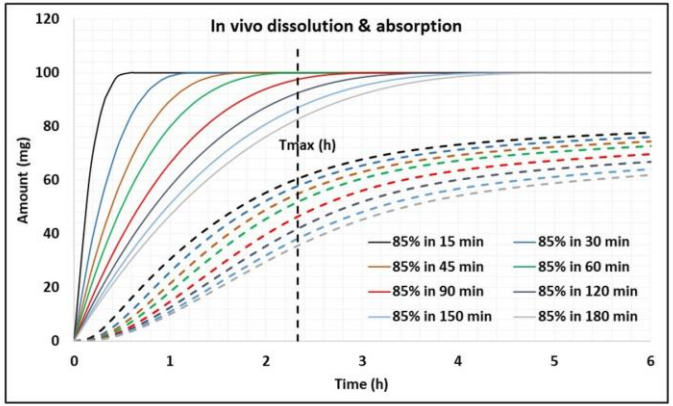
* observed T/R ratio's and CI's

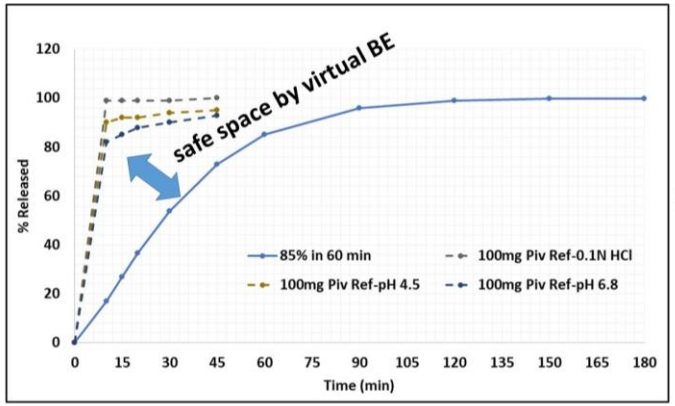
Biowaiver for both 100mg and 50mg – regulatory agency provided favorable feedback

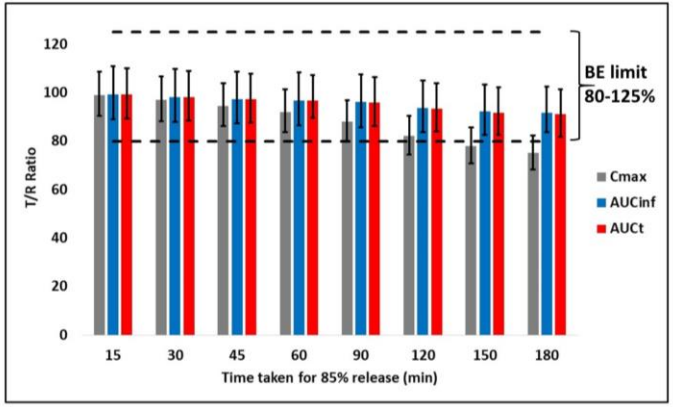
Cost, time savings, early launch

Case study#2: Biowaiver for study leverage, f2 failure



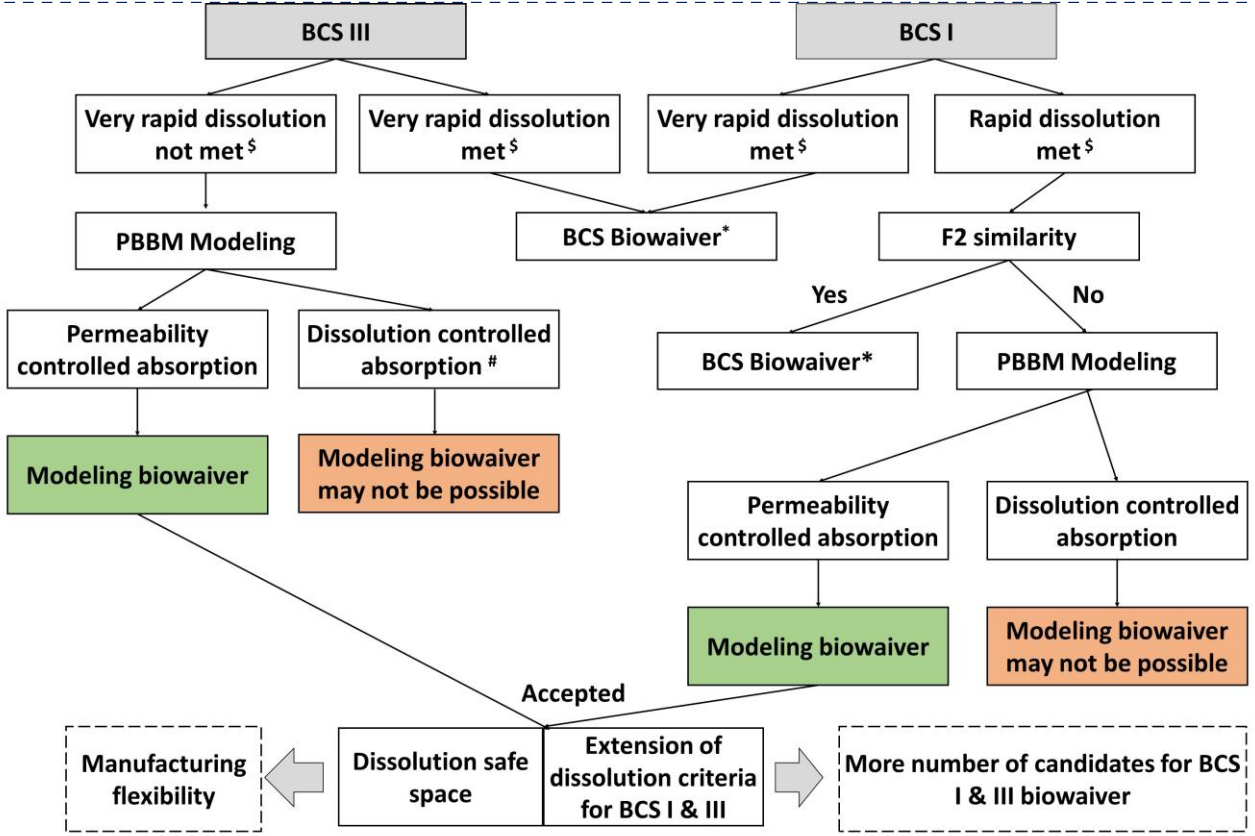






BE safe space of 85% in 60 min was determined without impacting bioequivalence

Case study#2: Biopharmaceutics risk assessment strategy for BCS I, III biowaivers



* Provided other criteria for biowaiver is met as per ICH M9

$ very rapid dissolution (>85% in 15 min), rapid dissolution (>85% in 30 min)

May not be applicable for BCS III

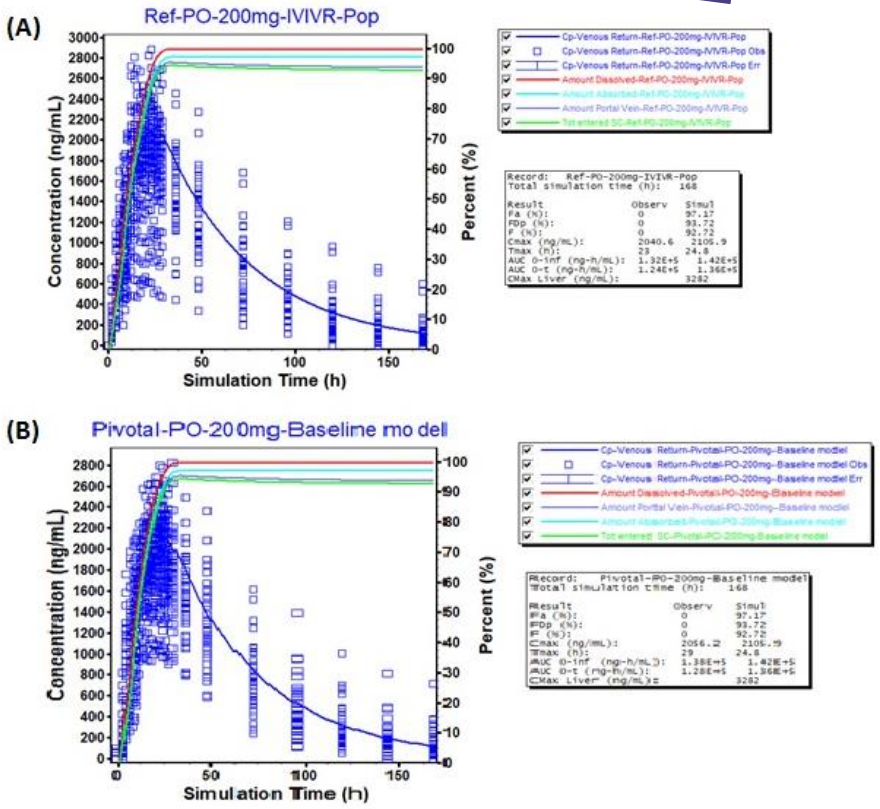
Case study#3: Dissolution specifications justification for ER formulation

- Product is formulated as extended release, with three time point specification
- Proposal was made to revise dissolution specifications at 7 h in order to relax ±20% to ±25% considering commercial and stability studies
- USFDA IVIVC guidance only allows ±20% deviation at each time point and thus justification was required for higher range
- PBBM modeling was used to justify the dissolution specifications through virtual BE and IVIVC/R

Specification time point	Existing specifications	Revised specifications
2 h	≤10%	≤10%
3 h	≥5%, ≤20%	≥5%, ≤20%
5 h	≥25%, ≤50%	≥25%, ≤50%
7 h	**≥50%, ≤70%**	**≥45%, ≤70%**
12 h	≥80%	≥80%

Case study#3: Dissolution specifications justification for ER formulation

Pivotal study validation of Reference (A) and Test (B)



Virtual Disso profiles generated at low profile (LP) and single point lower profile (SPLP)

Time (hrs)	Reference	Pivotal	LP	SPLP
2	4.00	2.00	1.00	2.00
3	10.00	13.00	7.00	13.00
4	22.00	27.00	22.00	27.00
5	35.00	40.00	29.00	40.00
7	61.00	63.00	48.00	45.00
9	80.00	80.00	77.00	80.00
12	98.00	97.00	91.00	97.00
15	101.00	101.00	100.00	101.00

Parameter	Geometric Means		% Geometric Mean Ratio	(90 % CI)
	Test	Reference		
Hypothetical Test Batch (Low Profile)				
C_{max}	1957.6	1978	98.97	91.86 - 106.64
$AUC_{0\text{-}inf}$	123000	122000	100.30	90.90 - 110.74
Hypothetical Test batch (Single Point Low)				
C_{max}	2031.2	1978	102.70	95.42 - 110.52
$AUC_{0\text{-}inf}$	124000	122000	101.20	91.73 - 111.63

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	Include product quality attributes in the model and provide justification (e.g. DT, hardness impact through dissolution)
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, 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
- Overall, more and more regulatory agencies are open to such submissions, knowledge sharing mainly in terms of regulatory justifications is required across academia, industry and agency

Acknowledgements

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- DRL 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
- Simulation Plus Team for giving me the opportunity

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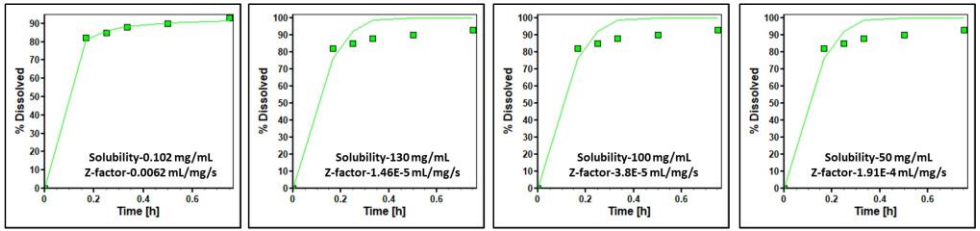
Thank You

BACKUP

PBBM Modeling

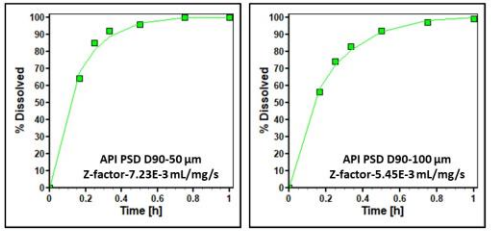
Dissolution data (solubility, volume, dose) → Calculate z-factor → Evaluate z-factor fitting → Check impact of solubility, time points, shape → Validate with multiple formulations

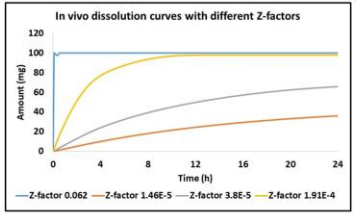
(a) Impact of solubility on z-factor & *in vivo* performance



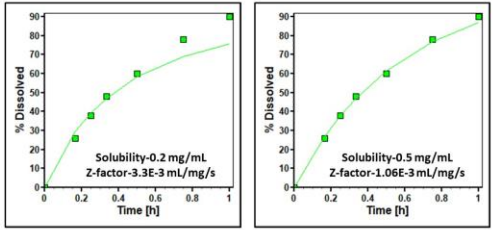
In vivo dissolution

(b) PSD impact through Z-factor

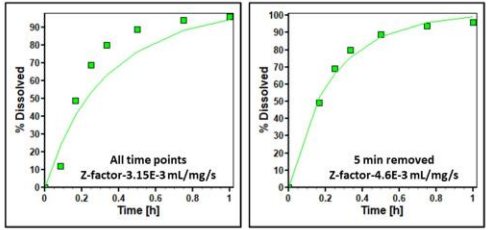




(c) Impact of fit on Z-factor



(d) Impact of specific time point on Z-factor



PBBM Modeling

Develop model for MR formulation

Input physchem, elimination kinetics

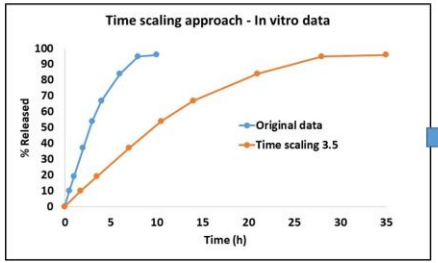
Direct disso input & Weibull (single, double, triple)

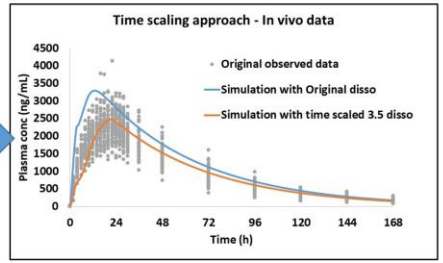
Evaluate Predictions

Alternatively evaluate time-scaling / IVIVR

Validate with multiple formulations

(a) Simple time scaling with Weibull

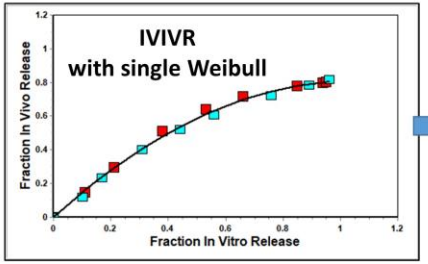


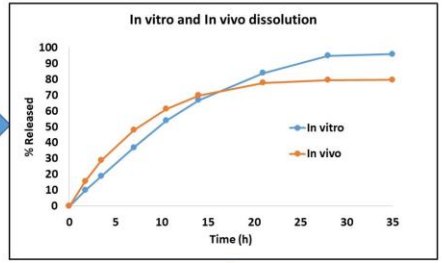


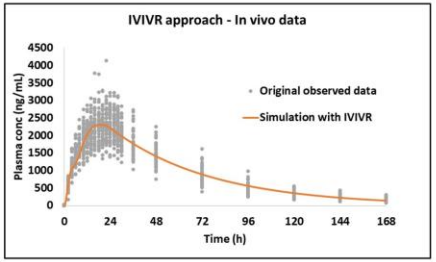
(b) IVIVR based time scaling

IVIVR

In vivo dissolution = function(In vitro dissolution)







Prediction with in vivo dissolution

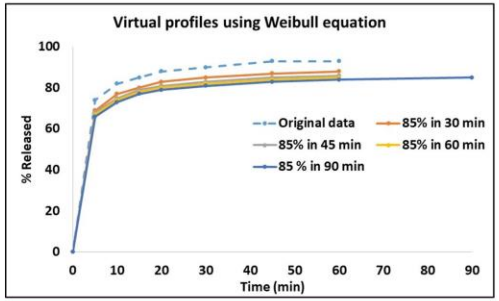
PBBM Modeling

(a)

Fit original dissolution data to Weibull (single/double/triple)

Use same shape factor, adjust extent to get required release

Virtual profiles with different release rates

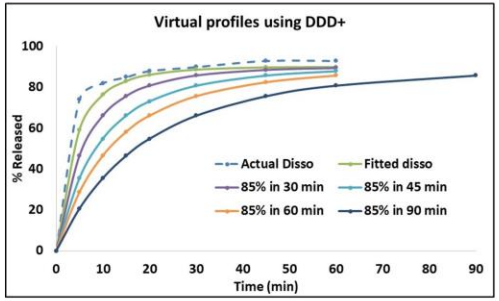


(b)

Develop DDD+ model with formulation, API inputs

Optimize calibration constant to match release

Generate virtual profiles with different calibration constants

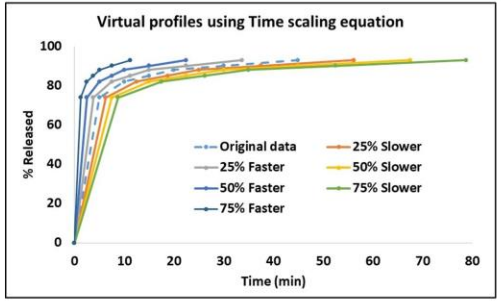


(c)

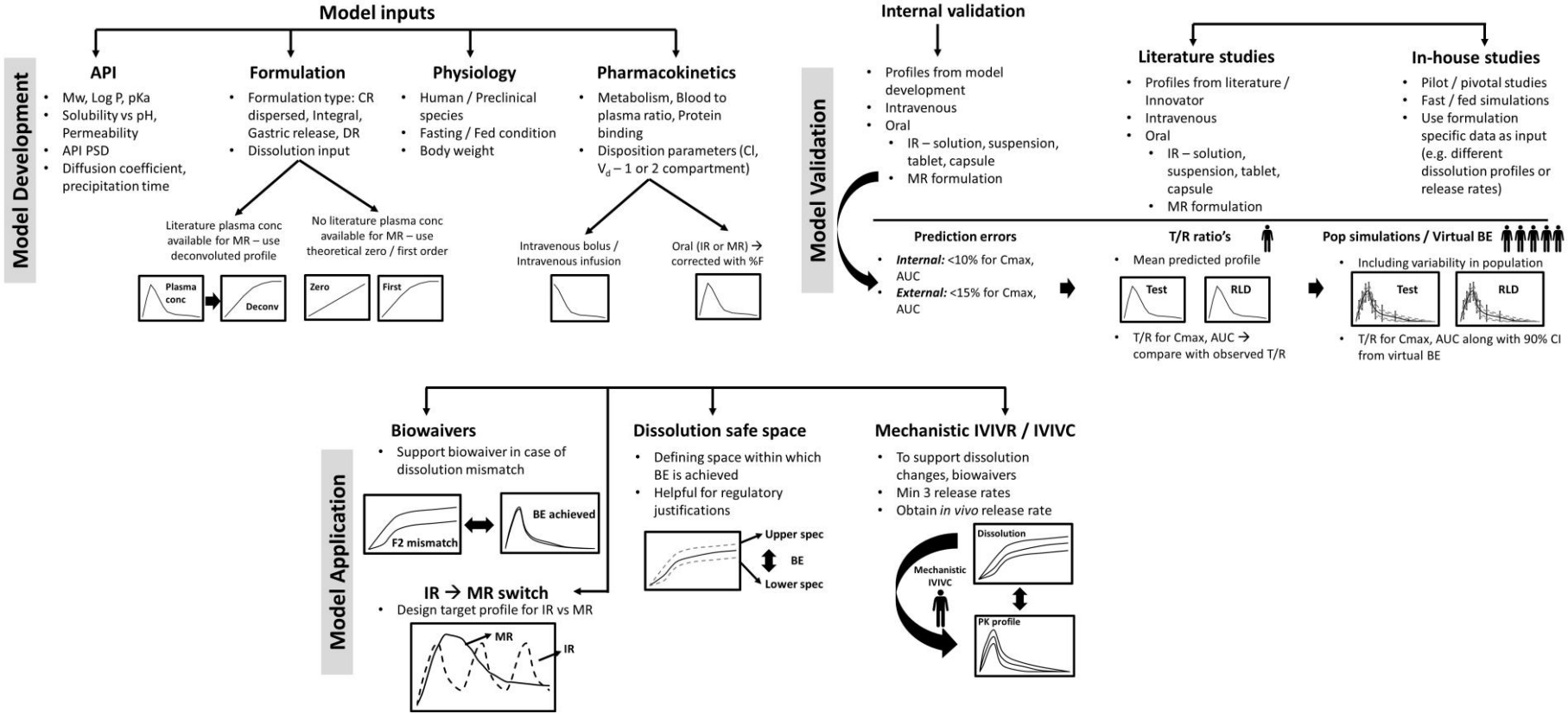
Original dissolution data

Time scaling eq. to generate slower/faster profiles

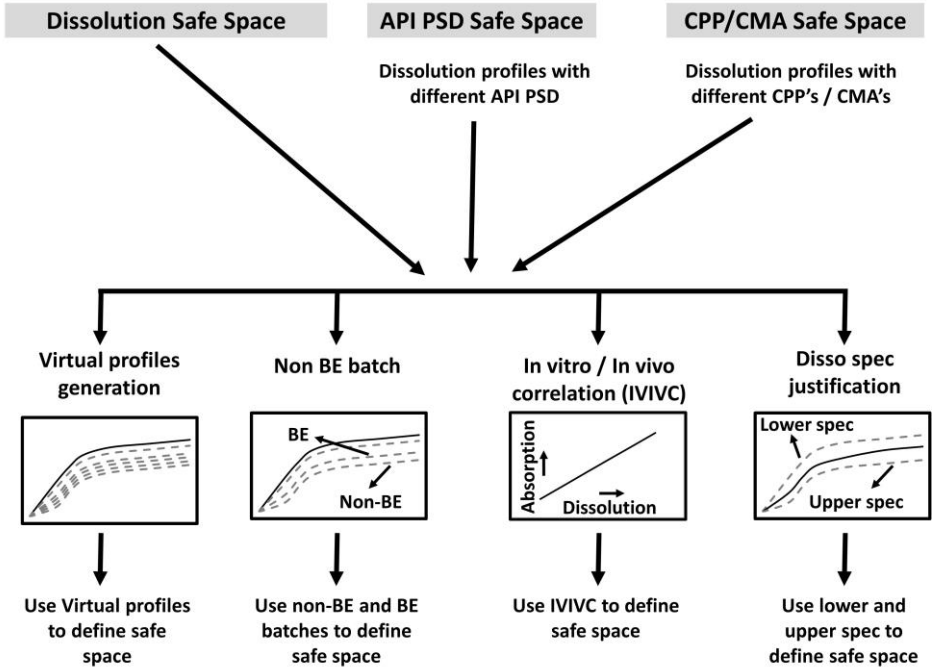
Virtual profiles with different release rates



MR formulation development using PBBM modeling

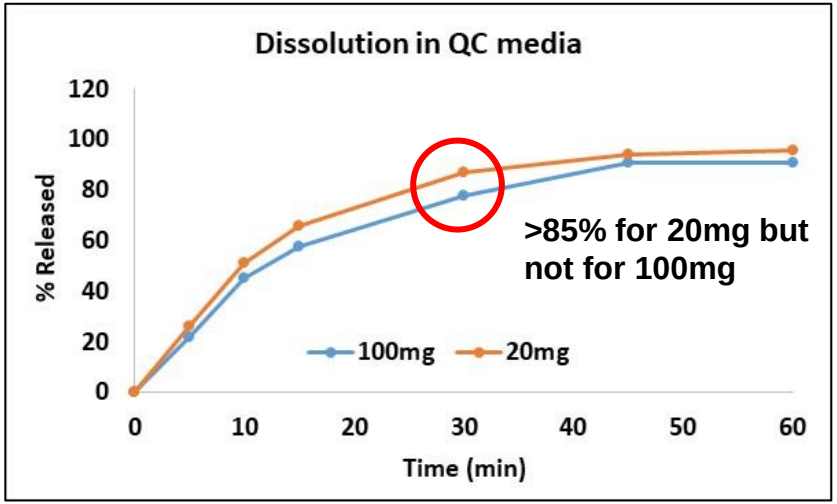


Safe space using PBBM



Case study: Biowaiver of lower strength of Dasatinib tablets with PBBM modeling

- Weakly basic molecule with pH dependent solubility (high in acidic and extremely poor in basic)
- Full replicate study was conducted on higher strength 100mg, waiver requested for 20mg based on comparative dissolution in QC media
- Despite matching f2 (59), it was found that release was rapid for 20mg (87% in 30 min), whereas it was not rapid for 100mg (78% in 30 min)
- Agency denied biowaiver, asked to conduct BE study on 20mg

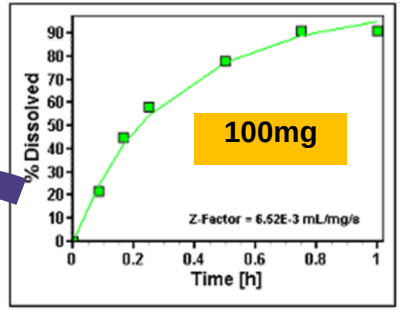


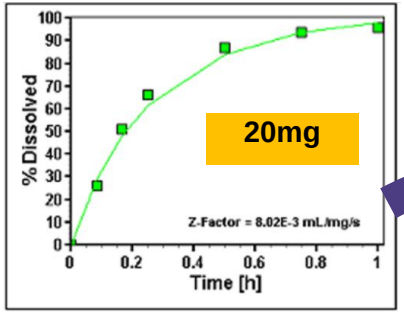
PBBM modeling was used to support waiver of complicated 20mg study: faster dissolution profile of 20mg used for 100mg simulations using z-factor

Case study: Biowaiver of lower strength of Dasatinib tablets with PBBM modeling

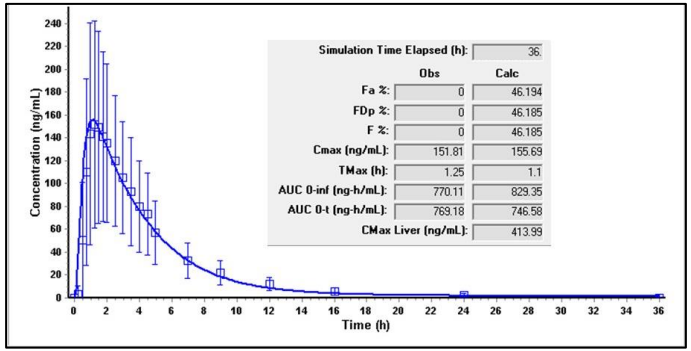
Dr.Reddy's

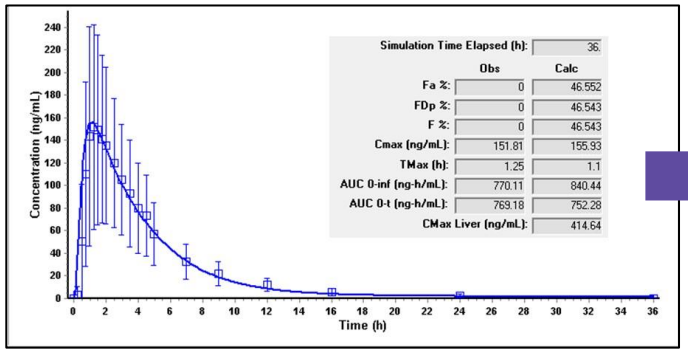
100mg validation





20mg input to 100mg model





Cost, time savings, early launch

PK Parameter	T/R [Faster disso of 20mg / 100mg]
Cmax (ng/mL)	100.15
AUCt (ng.h/mL)	101.34
AUCinf (ng.h/mL)	100.76

No impact of faster dissolution profiles on BE, biowaiver for 20mg was granted