FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling, PBBM Best Scientific Practices to Drive Drug Product Quality: Latest Regulatory and Industry Perspectives

Physiologically Based Biopharmaceutics Modeling (PBBM) Case Studies

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CERSI
University of Maryland

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FDA U.S. FOOD & DRUG ADMINISTRATION

PBBM (Subset of PBPK) Examples in Oral Formulation Development

CPP's, CMA's Impact on Dissolution CQA and PK

SUPAC based Biowaivers

pH-mediated DDI prediction

API PSD specification & justification

PK in Specific Populations: RI, HI, Pediatrics

PBPK In Drug Development

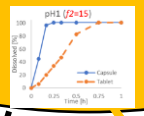
Dissolution profile dissimilarity / F2 mismatch Overide

PBBM for Drug Product Quality Applications, Innovator & Generic Industry

PBPK for Oral Biopharmaceutic Applications

Dev. Clinically Relevant Disso. specifications (CRDS)

DME, Enzyme mediated DDI Etc.



Dissolution BE safe space (internal/external decisions)

Biowaiver of lower strength

BE assessment between RLD and Test

Food effect prediction & BE

Modified from: Yuvaneshwari K., Kollipara, S. et al., Journal of Drug Delivery Science and Technology, 2022. **69**: p. 103152

Wu, Heimbach et.al, Pharm Res. 2022 Jul 15. doi: 10.1007/s11095-022-03319-6.

T0930-07-38

Dissolution Bioequivalence Safe Space Assessment of Molnupiravir and NHC Using Physiologically Based Biopharmaceutics Modeling

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PURPOSE

Molnupiravir (MOV; MK-4482, EIDD-2801) is an oral antiviral that has received emergency use authorization by the FDA for the treatment of adults with mild-to-moderate COVID-19. MOV is a prodrug of N-hydroxycytidine (NHC; formerly EIDD-1931) which inhibits viral replication of SARS-CoV-2. MOV is classified as a BCS Class I compound (high solubility, high permeability). While MOV showed low permeability with the Caco-2 cell model, the rat intestinal perfusion model showed that MOV has higher permeability than metoprolol. The bioequivalence safe-space was to be established for different formulations.

METHODS

To characterize human MOV absorption and systemic pharmacokinetics (PK) of NHC and to assess the bioequivalence of batches from three manufacturing sites, physiologically based biopharmaceutics modeling (PBBM) was undertaken using a dissolution method as per FDA guidance document. The developed models were qualified against the clinically observed results (Painter et al. 2021 study).

The intestinal permeability values of MOV were evaluated in a validated rat intestinal perfusion model. MOV was estimated to have a higher human Peff than metoprolol. MOV and metoprolol Peff values were calculated to be 2.16 x 10-4 cm/s and 1.5 x 10-4 cm/s, respectively from rat Peff data (Table 1, below). Given the higher permeability compared to the metoprolol marker with a human fraction absorbed of 95%, MOV is a high permeability compound.

Compound	Measured Rat ieiunal Peff ($\times 10^{-5}$ cm/sec) (mean ± SD)	Projected Human ieiunal Peff ($\times 10^{-4}$ cm/sec)
Metoprolol (High Permeability Reference)	3.69 ± 0.32 (n=4)	1.5
MOV (MK-4482)	4.55 ± 2.09 (n=4)	2.16

The dissolution curves obtained for capsule clinical batch and capsule reference batches, and other manufacturing batches using a USP 2 method are used together with the in vitro dissolution conditions (volume, solubility in the dissolution medium, and dose) to calculate Z-factors on the basis of Takano et al.

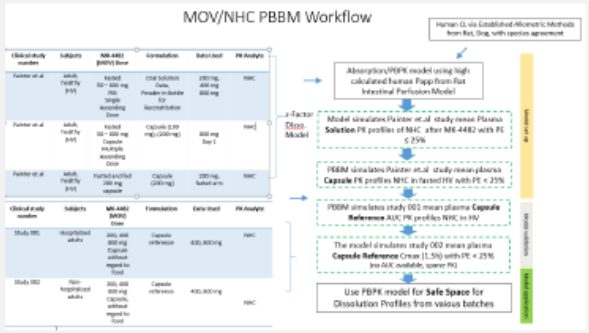
$$\frac{dX_{d,vitro}}{dt} = zX_{0,vitro}\left(X_{s,vitro}/X_{0,vitro}\right)^{2/3}\left(C_s - X_{d,vitro(t)}/V_{vitro,vitro}\right)$$

$z = \frac{3Dw}{\rho hr}$, where Dw is the diffusion coefficient, ρ is the density of the dissolving drug particles (after disintegration), r is the spherical particle radius of particles in the compartment (initial or current depending on user selection) and h is the diffusion layer thickness. Xd,vitro(t) is the mass of dissolved drug at time t, ρ is the density of the drug, Xs,vitro(t)is the mass of solid drug at time t, X0,vitro is the initial mass of solid drug, C_s is the saturated solubility of the drug, and Vvitro is the volume of the dissolution medium.

The z-factor calculation tool in GastroPlus was used, and the results of z-factors from in vitro data were used for the simulation by setting the dissolution model as z-factor model in GastroPlus. The dosage form was set as "IR tablet" or "IR capsule" in GastroPlus based on the dosing formulation.

For PBBM, GastroPlus v.9.8 was used, which included MOV permeability and solubility data. The solubility of MOV is 46 mg/mL in water and ranges from 43 mg/mL to 89 mg/mL in pH 1.2 to 8 buffer at 37oC. MOV solubility was 89 mg/mL at pH 1.2, 43 mg/mL at pH 4.9 and 52 mg/mL at pH 6.8.

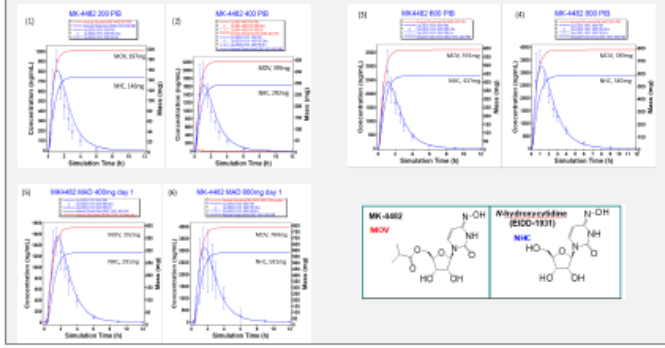
The PBBM workflow is shown below:



RESULTS

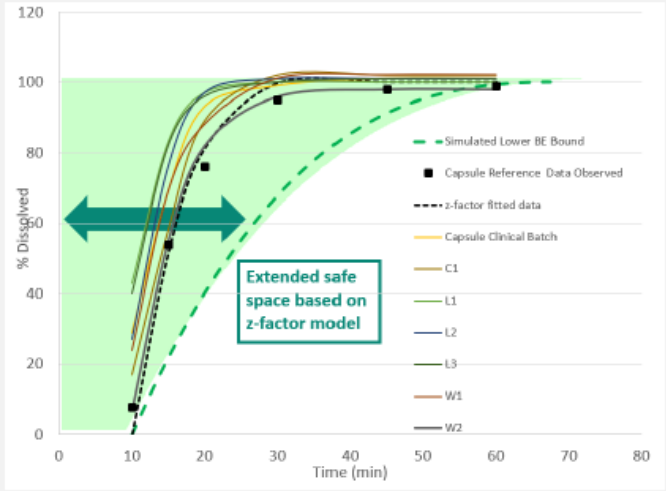
Panels 1-6 shows >85% absorption for MOV in both powder in bottle (PIB) reconstituted solution and capsule formulations. NHC is rapidly generated in vivo as demonstrated by early Tmax (~ 1-1.75h), and the amount of NHC reaching the systemic circulation indicates also Fa >85% after 200 mg, 400 mg, 600 mg or 800 mg MOV dosing as PIB (Panels 1-4) or capsule (Panels 5&6). The blue open squares in each plot are the clinically measured NHC levels. MOV (MK-4482) are typically not detected. PBBM predictive errors for Cmax and AUC were < 25%.

Simulated versus Observed NHC PK profiles for PIB Solution and Capsule Formulation in SAD and MAD studies (P004) after MOV (MK-4482) dosing.



RESULTS

Capsule Safe Space Dissolution Limits with the z-factor Model with Representative Clinical Batches from Different Manufacturing Sites with batches C1 through W2 using the Capsule Reference Batch.



CONCLUSION(S)

The proposed PBBM is suitable for applications to support, along with appropriate MOV dissolution data, potential future formulation changes post-approval.

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Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NCJE, Morin MJ, Szewczyk LJ, Painter GR. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. Antimicrob Agents Chemother. 2021 Mar 1;65(5):e02428-20. doi: 10.1128/AAC.02428-20. Epub ahead of print. PMID: 33649113; PMCID: PMC8092915.
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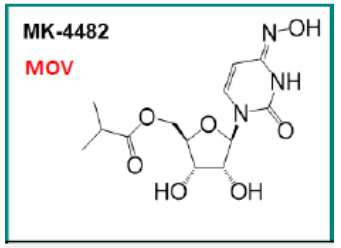
Molnupiravir (MOV) PBBM Model

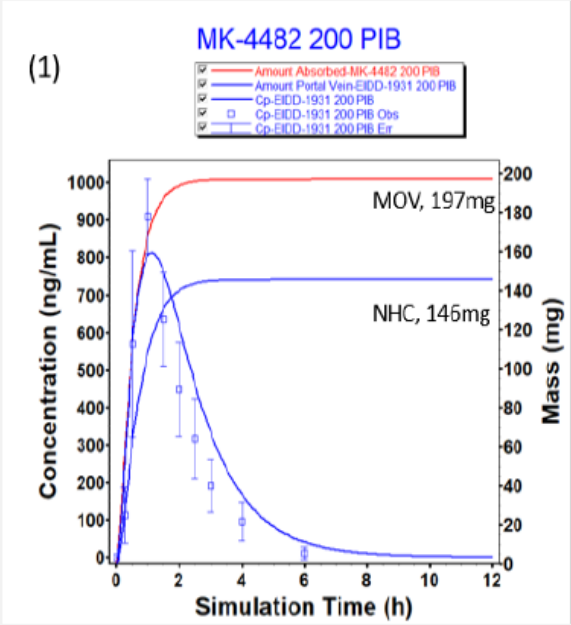


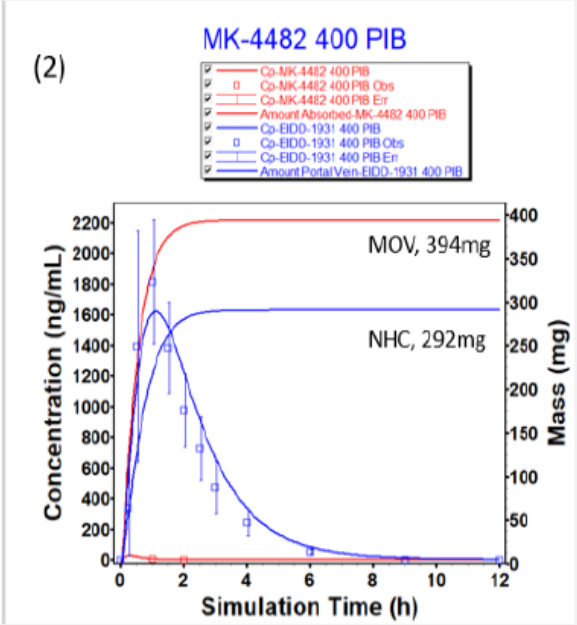
MOV has high permeability and solubility

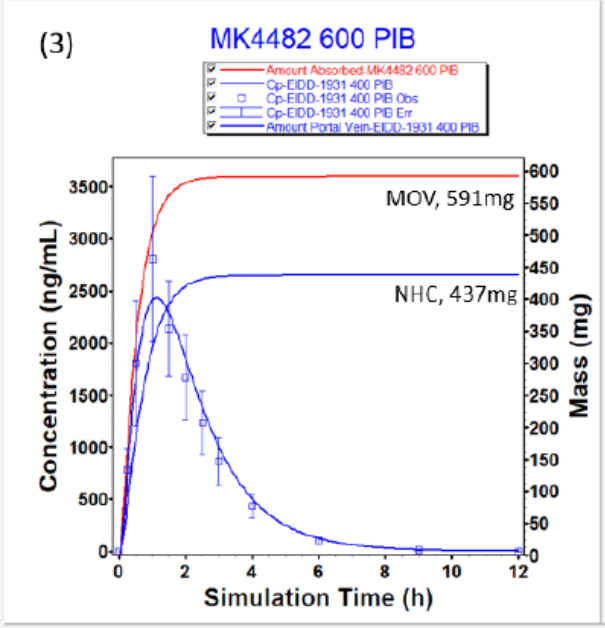
- To characterize human MOV absorption and systemic pharmacokinetics (PK) of NHC and to assess the bioequivalence of batches from three manufacturing sites, physiologically based biopharmaceutics modeling (PBBM) was undertaken using a dissolution method as per FDA guidance document. The developed models were qualified against the clinically observed results (Painter et al. 2021 study).
- The **solubility** of MOV is 46 mg/mL in water and ranges from 43 mg/mL to 89 mg/mL in pH1.2 to 8 buffer.
- The **intestinal permeability** values of MOV were evaluated in a validated rat intestinal perfusion model. MOV was estimated to have a higher human Peff than metoprolol. MOV and metoprolol Peff values were calculated to be 2.16 x 10-4 cm/s and 1.5 x 10-4 cm/s, respectively from rat P_{eff} data. Given the higher permeability compared to the metoprolol marker with a human fraction absorbed of 95%, MOV is a high permeability compound.

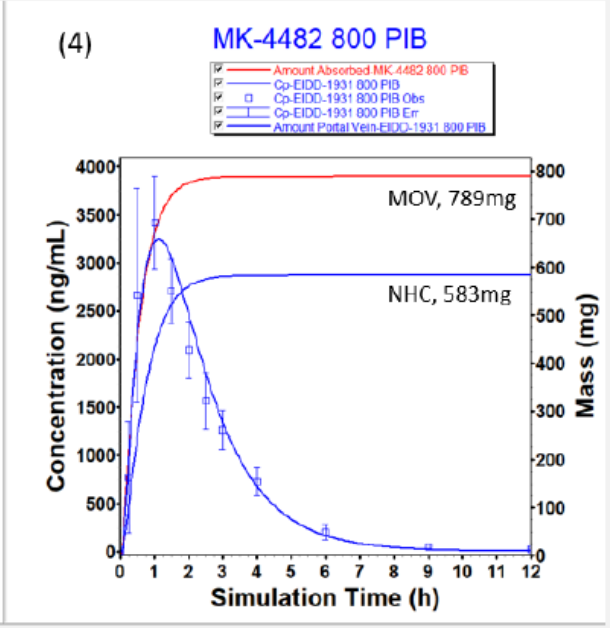
Compound	Measured Rat jejunal P_{eff} ($x10^{-5}$ cm/sec) (mean ± SD)	Projected Human jejunal P_{eff} ($x10^{-4}$ cm/sec)
Metoprolol (High Permeability Reference)	3.69 ± 0.32 (n=4)	1.5
MOV (MK-4482)	4.55 ± 2.09 (n=4)	2.16

PBBM PIB Solutions

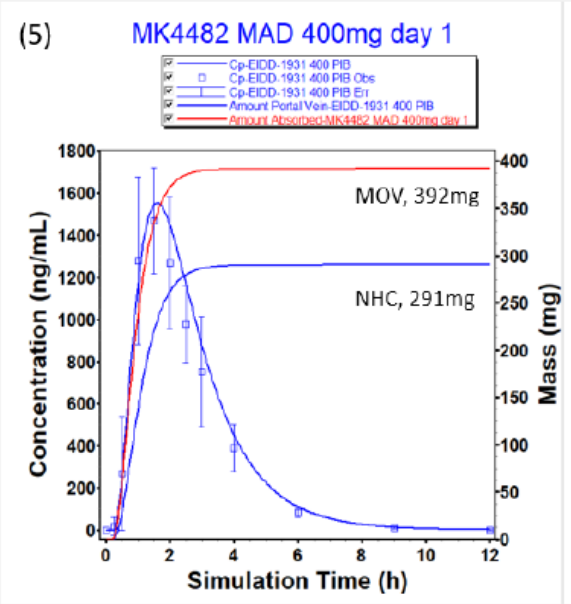


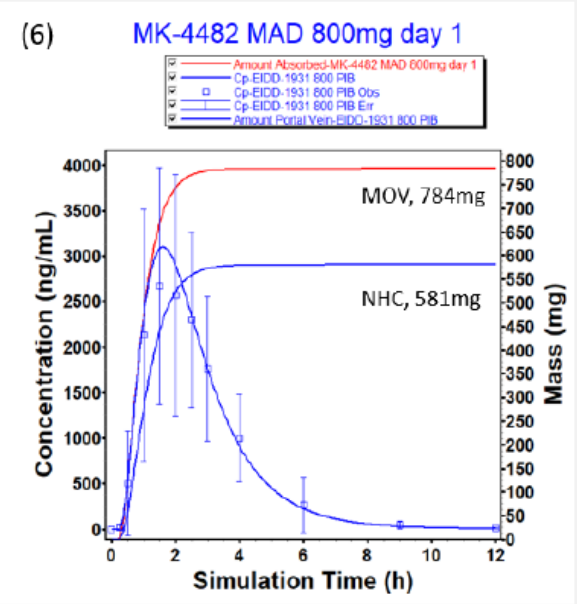


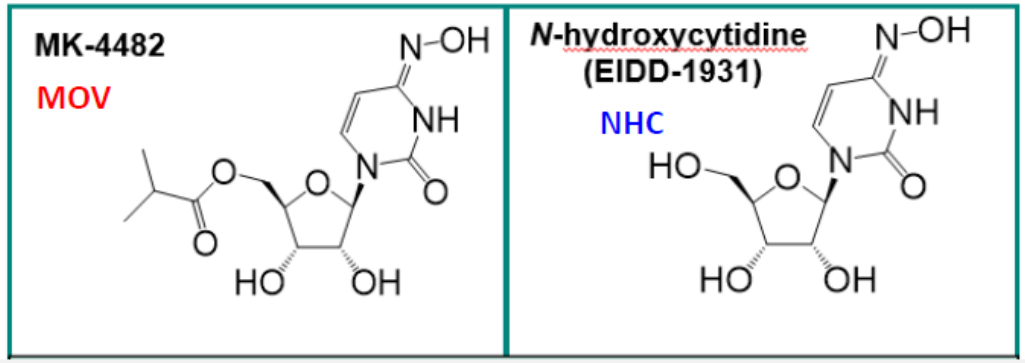




PBBM Capsule Data







Molnupiravir

MOV/NHC PBBM Workflow

Clinical study number	Subjects	MK-4482 (MOV) Dose	Formulation	Data Used	PK Analyte
Painter et.al	Adult, healthy (HV)	Fasted 50 – 800 mg PIB Single Ascending Dose	Oral Solution Data, Powder in Bottle for Reconstitution	200 mg, 400 mg 800 mg	NHC
Painter et.al	Adult, healthy (HV)	Fasted 50 – 800 mg Capsule Multiple Ascending Dose	Capsule (100 mg), (200 mg)	800 mg Day 1	NHC
Painter et.al	Adult, healthy (HV)	Fasted and fed 200 mg capsule	Capsule (200 mg)	200 mg, fasted arm	NHC

z-Factor Disso. Model

Clinical study number	Subjects	MK-4482 (MOV) Dose	Formulation	Data Used	PK Analyte
Study 001	Hospitalized adults	200, 400 800 mg Capsule without regard to food	Capsule reference	400, 800 mg	NHC
Study 002	Non-hospitalized adults	200, 400 800 mg Capsule, without regard to food	Capsule reference	400, 800 mg	NHC

Human CL via Established Allometric Methods

Absorption/PBPK model using high calculated human Papp from Rat Intestinal Perfusion Model

Model simulates Painter et.al study mean Plasma **Solution** PK profiles of NHC after MK-4482 with PE ≤ 25%

PBBM simulates Painter et.al study mean plasma **Capsule** PK profiles NHC in fasted HV with PE < 25%

PBBM simulates study 001 mean plasma **Capsule Reference** AUC PK profiles NHC in HV

The model simulates study 002 mean plasma **Capsule Reference** Cmax (1.5h) with PE < 25% (no AUC available, sparse PK)

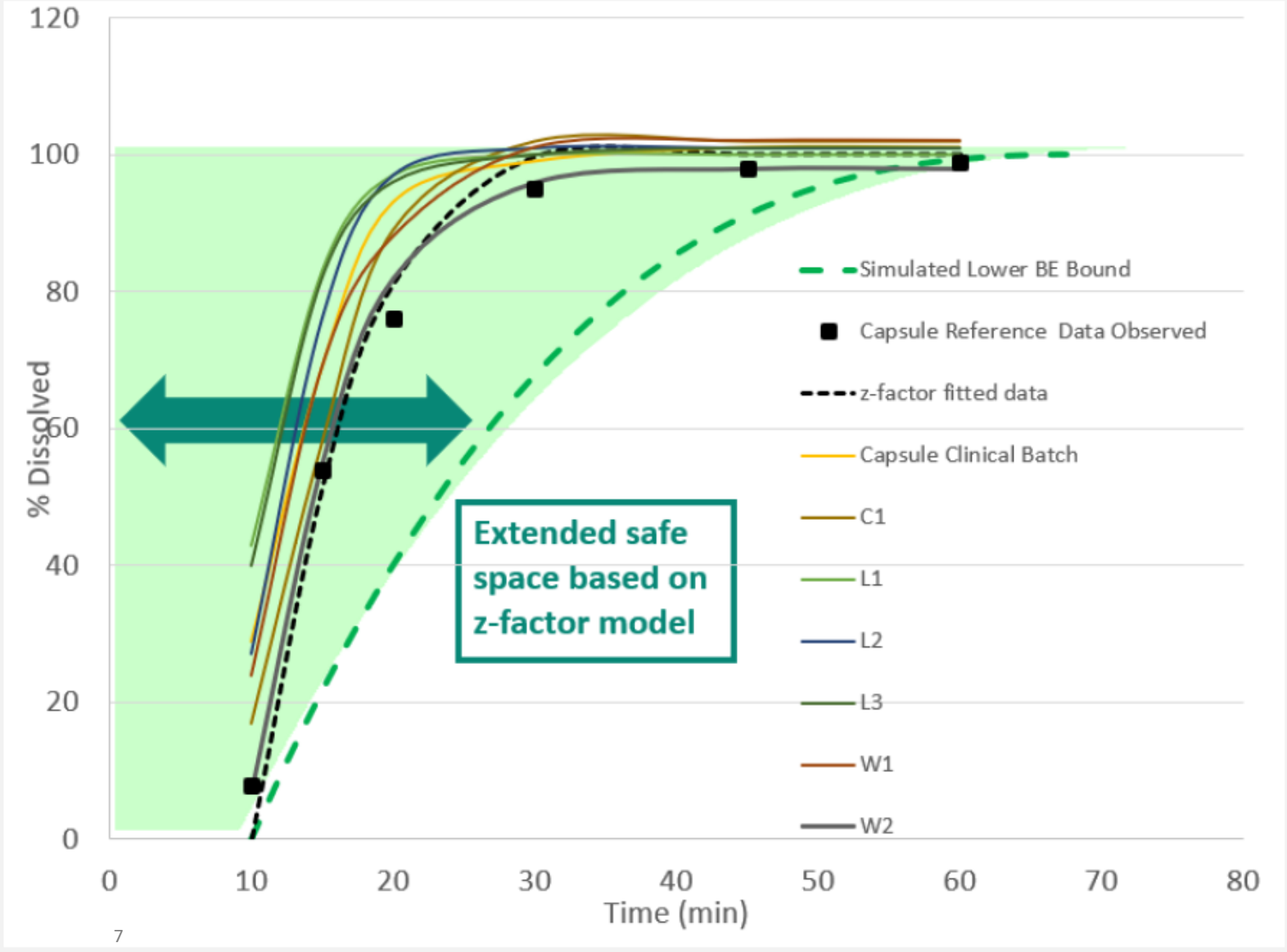
Use PBPK model for **Safe Space** for Dissolution Profiles from various batches

Model set up

Model validation

Model application

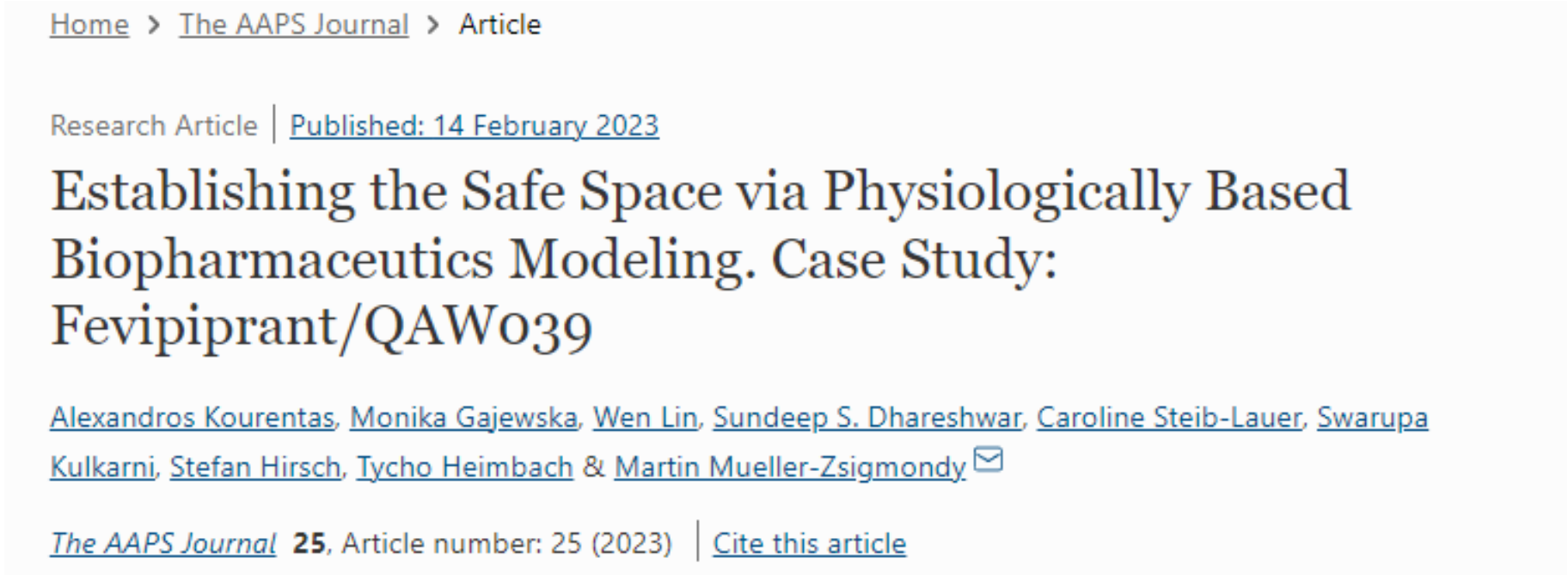
Capsule Safe Space Dissolution Limits with the z-factor Model with Representative Clinical Batches from Different Manufacturing Sites with batches C1 through W2 using the Capsule Reference Batch.



Dissolution Model: z-factors from in vitro data were used for the simulations by setting the dissolution model as z-factor model

=> All Batches from 3 Manufacturing Sites (C), (L), (W) are BE as they are in the Safe Space

Case Study: PBBM BE Safe Space for Fevipiprant



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Research Article | Published: 14 February 2023

Establishing the Safe Space via Physiologically Based Biopharmaceutics Modeling. Case Study: Fevipiprant/QAW039

Alexandros Kourentas, Monika Gajewska, Wen Lin, Sundeep S. Dhareshwar, Caroline Steib-Lauer, Swarupa Kulkarni, Stefan Hirsch, Tycho Heimbach & Martin Mueller-Zsigmondy

The AAPS Journal **25**, Article number: 25 (2023) | Cite this article

https://link.springer.com/article/10.1208/s12248-023-00787-5

Case Study: PBBM BE Safe Space for Fevipiprant

Purpose:

- PBBM to aid in specification setting for BCS IV drug for two doses with BE and observed non-BE data and IV micro-dosing data

Dissolution Method:

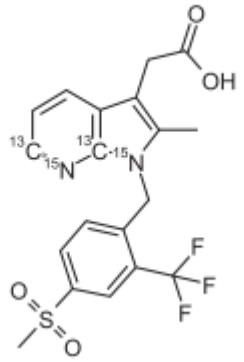
QC method, pH 6.8

Dissolution Model:

z-factor, Weibull

- **Other:**

IV Microdosing was used



Fevipiprant – BCS IV drug

- Fevipiprant is a zwitterionic, low molecular weight, BCS class IV drug substance. PBBM were performed to assess the impact of in vitro dissolution on the in vivo performance of immediate release film coated tablets during development and scaling-up to commercial scale.

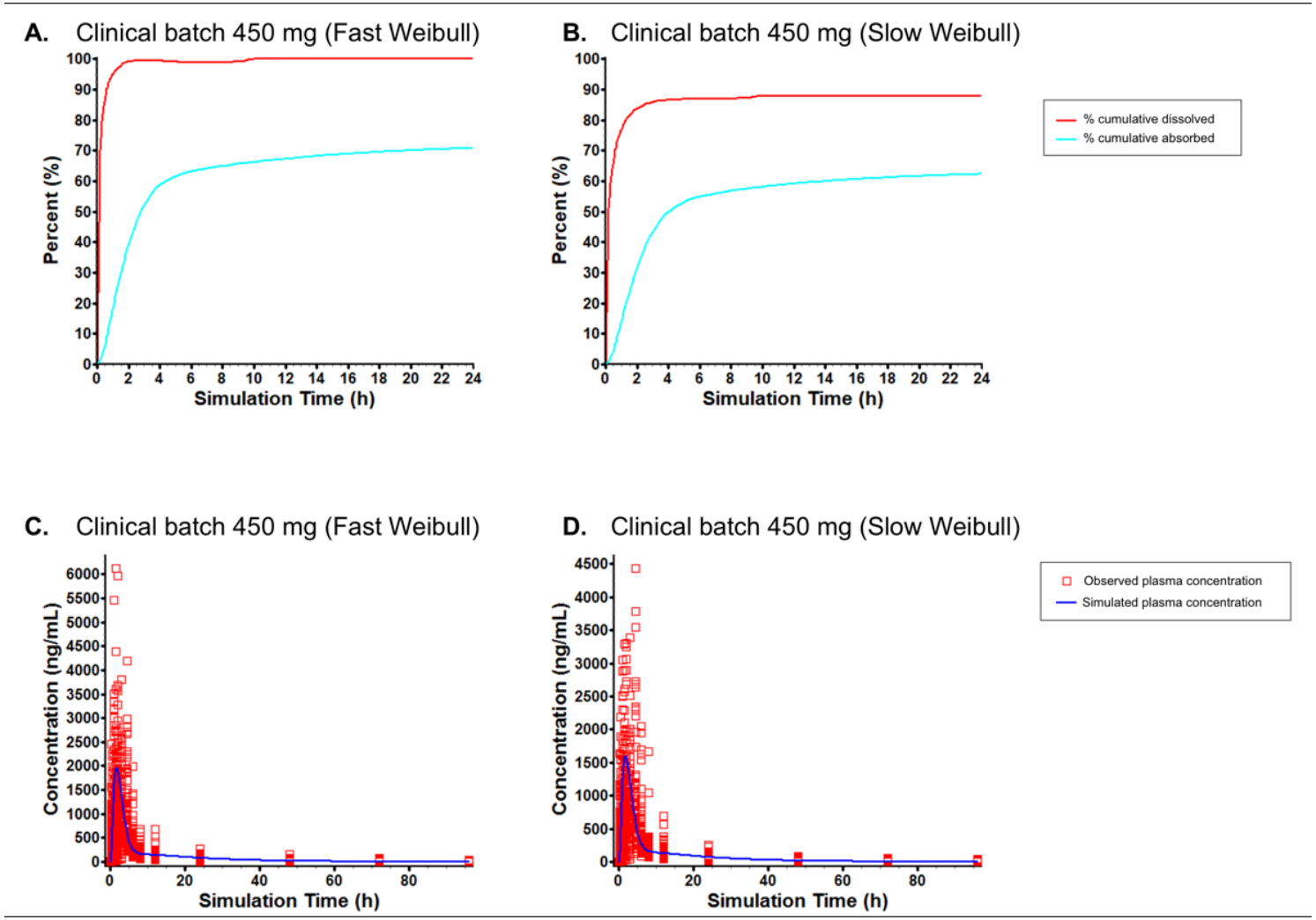
- A fevipiprant dissolution safe space was established using observed clinical intravenous and oral PK data from bioequivalent and non-bioequivalent formulations. Quality control dissolution profiles with tablets were used as GastroPlusTM model inputs to estimate the in vivo dissolution in the gastrointestinal tract, and to simulate human exposure.

- The PBBM performance was demonstrated for various oral dosage forms (150 – 500 mg), including the non-bioequivalent batches in fasted healthy adults. To define the safe space at 450 mg, simulations were performed using theoretical dissolution profiles.
- A specification of Q= 80% dissolved after 60 min for an immediate release oral solid dosage form reflected the boundaries of the safe space. The dissolution profile of the 450 mg commercial-scale batch was within a dissolution region where bioequivalence is anticipated, not near an edge of failure for dissolution, providing additional confidence to the proposed acceptance criteria. The safe space allowed for a wider than 10% dissolution difference for bioequivalent batches, superseding f2 similarity analyses.

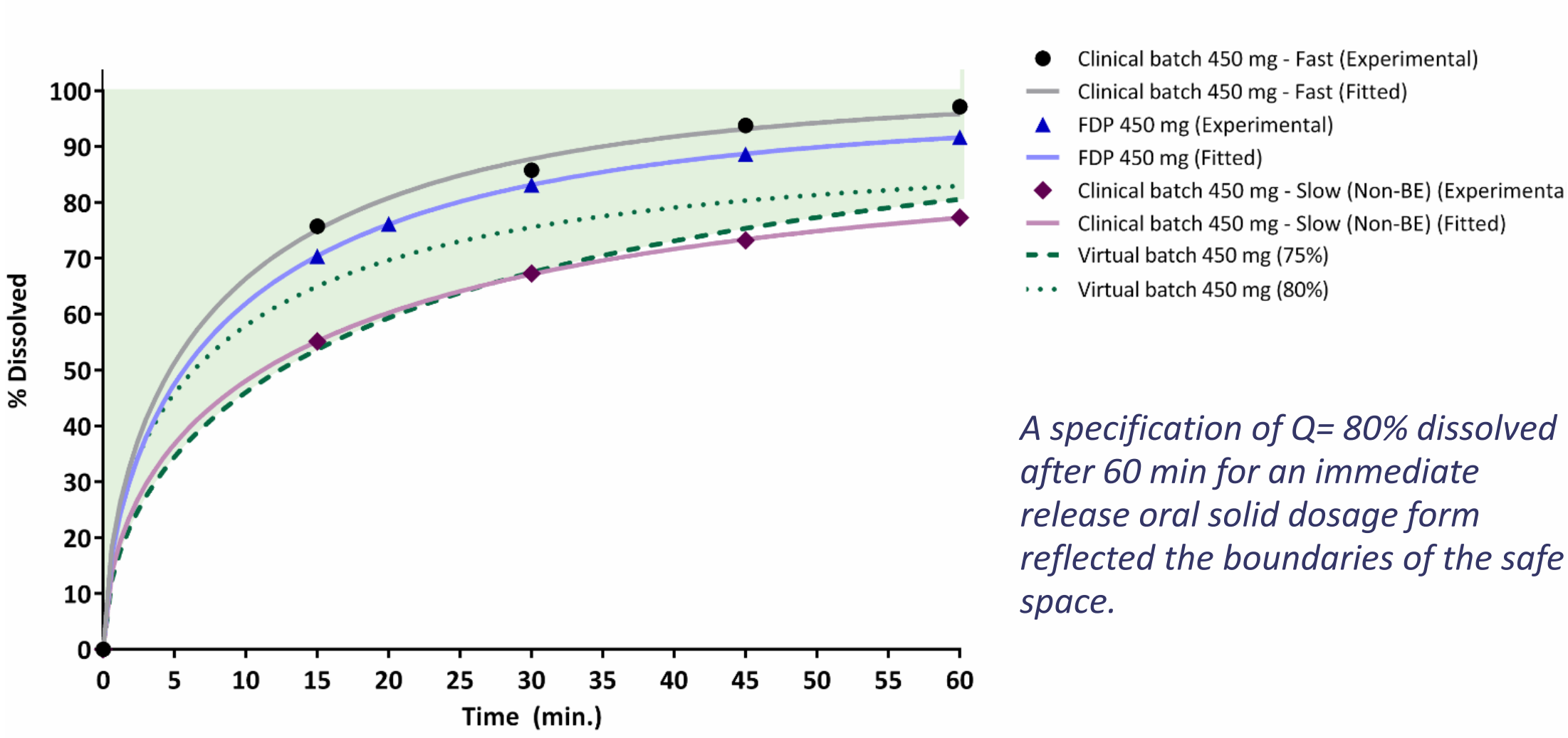
Fevipiprant PBBM with Microdosing and Different Dose Strength

Model setup	• Develop model to fit IV data	← *fevipiprant i.v. microdose following oral administration at 150 mg to fasted healthy adults*
	• Select dissolution model	← *z factor and Weibull fitting of QC dissolution data*
	• Explore oral absorption	← *PhysChem properties, permeability, & solubility* ← *PSA analysis of precipitation time and solubilization ratio*
Model qualification	• Simulate drug exposure data obtained at 150 mg and 450 mg	← *fevipiprant oral administration to fasted healthy adults (Caucasian population)*
	• Validate virtual population at 450 mg	← *study with non BE tablet batches*
Model application	• Establish safe space	← development of virtual batches & performance prediction with VBE trials
	• Explore clinically relevant dissolution acceptance criteria	

Fevipiprant PK after 450 mg (fast, slow) Dissolution Batches



Fevipiprant PBBM Safe Space for Dissolution Specification Setting



A specification of Q= 80% dissolved after 60 min for an immediate release oral solid dosage form reflected the boundaries of the safe space.

Newer PBBM Case Studies

Wu, Heimbach et.al, Pharm Res. 2022 Jul 15. doi: 10.1007/s11095-022-03319-6.

Pharmaceutical Research
https://doi.org/10.1007/s11095-022-03319-6

EXPERT REVIEW

Physiologically Based Pharmacokinetics Modeling in Biopharmaceutics: Case Studies for Establishing the Bioequivalence Safe Space for Innovator and Generic Drugs

Di Wu[1] · Maitri Sanghavi[2] · Sivacharan Kollipara[3] · Tausif Ahmed[3] · Anuj K Saini[2] · Tycho Heimbach[1]

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Abstract
For successful oral drug development, defining a bioequivalence (BE) safe space is critical for the identification of newer bioequivalent formulations or for setting of clinically relevant in vitro specifications to ensure drug product quality. By definition, the safe space delineates the dissolution profile boundaries or other drug product quality attributes, within which the drug product variants are anticipated to be bioequivalent. Defining a BE safe space with physiologically based biopharmaceutics model (PBBM) allows the establishment of mechanistic in vitro and in vivo relationships (IVIVR) to better understand absorption mechanism and critical bioavailability attributes (CBA). Detailed case studies on how to use PBBM to establish a BE safe space for both innovator and generic drugs are described. New case studies and literature examples demonstrate BE safe space applications such as how to set in vitro dissolution/particle size distribution (PSD) specifications, widen dissolution specification to supersede *f2* tests, or application toward a scale-up and post-approval changes (SUPAC) biowaiver. A workflow for detailed PBBM set-up and common clinical study data requirements to establish the safe space and knowledge space are discussed. Approaches to model in vitro dissolution profiles i.e. the diffusion layer model (DLM), Takano and Johnson models or the fitted PSD and Weibull function are described with a decision tree. The conduct of parameter sensitivity analyses on kinetic dissolution parameters for safe space and virtual bioequivalence (VBE) modeling for innovator and generic drugs are shared. The necessity for biopredictive dissolution method development and challenges with PBBM development and acceptance criteria are described.

Keywords bioequivalence safe space · f2 test · physiologically based pharmacokinetic modeling (PBPK) · physiologically based biopharmaceutics modeling (PBBM) · in vitro dissolution

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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Establishing the Bioequivalence Safe Space for Immediate-Release Oral Dosage Forms using Physiologically Based Biopharmaceutics Modeling (PBBM): Case Studies

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- Key contributor to 15+ IND's and 5 NDAs for currently marketed drug products
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