PBPK Modeling to Support General and Product-Specific Guidance Development

2026 AGDD Webinar: Leveraging Model-Integrated Evidence (MIE) in the Development & Approval of Generic Drugs

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Disclaimer

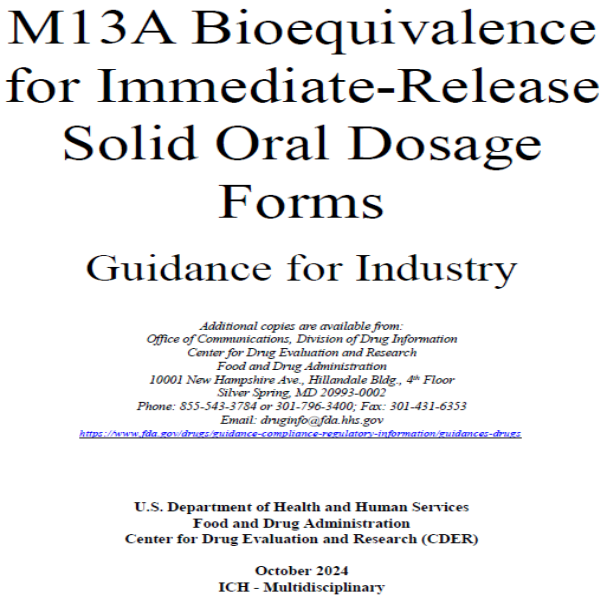
This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

Outline

- PBPK to support general guidance development
- PBPK to support product specific guidance development

PBPK: Physiologically-based pharmacokinetic modeling

ICH M13A Guideline Supported by PBPK Regulatory Applications and Research



M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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

October 2024
ICH - Multidisciplinary

Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms (Issued October 2024)

5. Fasting and Fed Study Conditions (2.1.5)

"High risk products"… both fasting and fed studies are needed if not otherwise justified. Such a justification may be supported by, *e.g.,* differences in formulations including qualitative and/or quantitative difference(s) in excipients, the BCS classification of the drug substance, *in vitro* testing such as disintegration and dissolution testing in biorelevant media, pilot study(ies), and modeling, such as validated physiologically-based pharmacokinetic (PBPK) modeling and simulation or semi-mechanistic absorption models, that is fit for the purpose. "

D. pH-Dependency (3.4)

"Modelling, e.g., appropriately validated/qualified PBPK modelling or semi-mechanistic absorption models, and virtual BE simulation may be used to further assess the risk of bioinequivalence. "

Case Example 1: Dabigatran PBPK Modeling to predict the effect of gastric pH on BE

Background: As a proof of concept, we have utilized an oral PBPK model of dabigatran etexilate capsule for assessing/ predicting the effect of gastric pH, e.g., concomitant use of acid reducing agents (ARA) on the BE of generic dabigatran etexilate capsule using virtual healthy subjects and virtual bioequivalence (VBE) trials.

Regulatory Research: Due to the unavailability of biorelevant dissolution, hypothetical biorelevant dissolution profiles were predicted based on available quality control (QC) dissolution (pH 4.5) for lability of biorelevant dissolution data, test product and reference standard. VBE using PBPK models were performed to assess the potential impact of gastric pH changes on the PK and BE of Dabigatran.

Results: The VBE results suggested around 30% reduction of drug exposure values for both test product and reference standard due to increased gastric pH (use of ARA) and demonstrated BE of dabigatran etexilate capsule under fasted condition with proton pump inhibitor (PPI) co-administration. The developed PBPK model is also able to capture the population differences (Caucasian VS Indian/Asian).

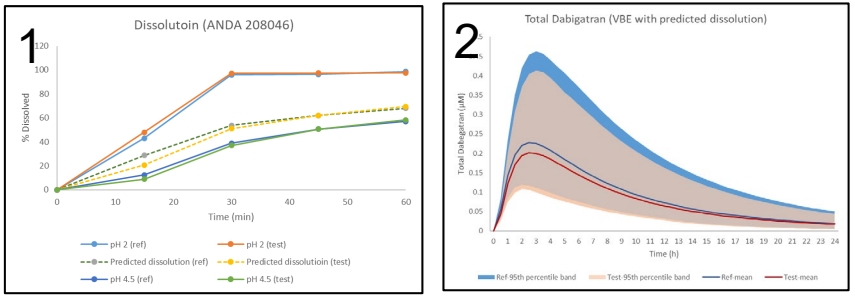


Figure: (1) QC dissolution profiles VS predicted hypothetical biorelevant dissolution profiles for the test and reference profiles based on QC dissolution profile (pH 4.5) (2) **VBE trials show that the test and reference Dabigatran capsules are BE under fasted condition and with pantoprazole co-administration**

Adopted from Arindom Pal poster presented at 2024 AAPS

Case Example 2 : PBPK to Evaluate Gastric pH Impact on BE of Palbociclib Tablets

Background: Palbociclib is a BCS Class II weak base drug that shows pH-dependent solubility. IBRANCE tablets (palbociclib immediate release (IR) tablets, NDA 212436), the reference listed drug (RLD**), contains a pH modifier** to help minimize the pH-effect in the presence of acid-reducing agents (ARAs). The current FDA product-specific guidance (PSG) for palbociclib IR tablets recommends conducting an additional fasting BE study in the presence of an ARA.

Purpose: To develop a PBPK model of palbociclib IR tablets to **identify biopredictive dissolution and assess the impact of co-administration of ARAs** on BE for palbociclib IR tablets.

Method :The PBPK models were developed using two different approaches for incorporating dissolution data: (1) fitting a **Z-factor** to dissolution data and (2) **directly using** dissolution data. The validated PBPK model was then used to predict PK and BE of generic palbociclib tablets in subjects administered with an ARA.

Results: The **direct dissolution incorporation** approach predicted BE of an approved generic palbociclib IR product under fasted conditions with the co-administration of an ARA **using available pH 4.5 dissolution data**. The presented models may be used to identify biopredictive dissolution and assess the impact of co-administration of ARAs on BE for generic palbociclib IR tablets.

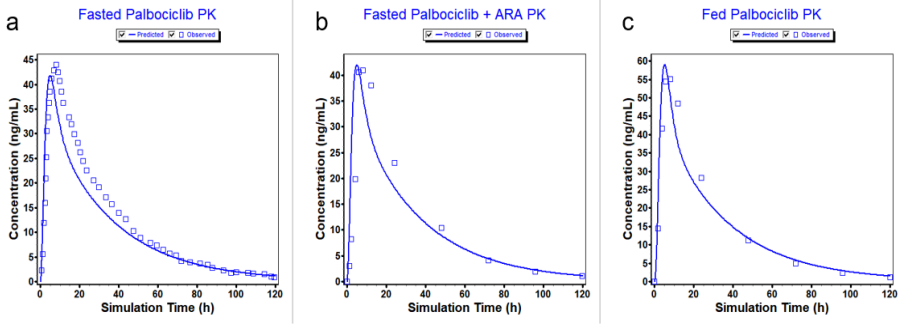


Fig 1. (a) Fasting, (b) fasting + ARA, and (c) Fed palbociclib predicted vs. observed (from NDA) PK.

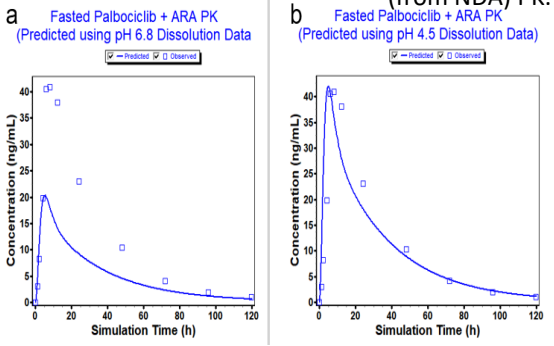


Fig 2. Fasting palbociclib + ARA PK prediction using (a) pH 6.8 dissolution data vs. (b) pH 4.5 dissolution data of RLD IR tablets

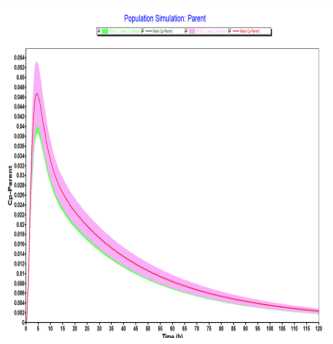


Fig 3. Representative VBE of fasting palbociclib + ARA using pH 4.5 dissolution data of Test and Reference IR tablets from ANDA #1

Adopted from Raqeeb Jamil poster presented at 2025 ASCPT

Cases 1 and 2 Summary

- A PBPK model can be used to predict BE of generic dabigatran and palbociclib IR tablet products with and without the co-administration of ARAs under the fasting condition.
- These validated PBPK models may be used to identify biopredictive dissolution and assess the impact of co-administration of ARAs on the BE of generic dabigatran and palbociclib IR tablets under the fasting condition.
- PBPK modeling regulatory research projects were conducted to support the development and implementation of ICH M13A general guidance in terms of providing justifications for waiving unnecessary in vivo BE study.

GDUFA Supported Relevant Research Projects

- Grant (U01FD007352) Development and Validation of a Best Practices Framework for PBPK Analysis for Biopharmaceutic Applications in Support of Model-Informed Biowaivers of Fed State BE Studies for BCS Class II Drugs with Rodrigo Cristofoletti at University of Florida
- Contract (75F40121C00020) Disintegration and Dissolution of Solid Dosage Forms and Influence of Food Induced Viscosity on its Kinetics, Tools and Methodologies for Bioequivalence and Substitutability Evaluation with Peter Langguth at Johannes Gutenberg University
- The above two research projects were conducted to support BE assessment for potential high-risk products per ICH M13A.

Outcome (Representative Publications):

- Rudolph N, Charbe N, Plano D, Shoyaib AA, Pal A, Boyce H, Zhao L, Wu F, Polli J, Dressman J, Cristofoletti R. *A physiologically based biopharmaceutics modeling (PBBM) framework for characterizing formulation-dependent food effects: Paving the road towards fed state virtual BE studies for itraconazole amorphous solid dispersions*. Eur J Pharm Sci. (2025) 209:107047. doi: 10.1016/j.ejps.2025.107047. Epub 2025 Feb 19. PMID: 39983931.
- *Umer MF, Stahl V, Al-Gousous J, Nawroth T, Sun WJ, Wu F, Jiang W, Gao Z, Langguth P. Food Effect and Formulation: How Soluble Fillers Affect the Disintegration and Dissolution of Tablets in Viscous Simulated Fed State Media. Pharmaceutics. (2025) 17(5):567. doi: 10.3390/pharmaceutics17050567. PMID: 40430859; PMCID: PMC12114628.*

Ref: FY 2025 GDUFA Science and Research Report | FDA

Control of Nitrosamine Impurities in Human Drugs Guidance

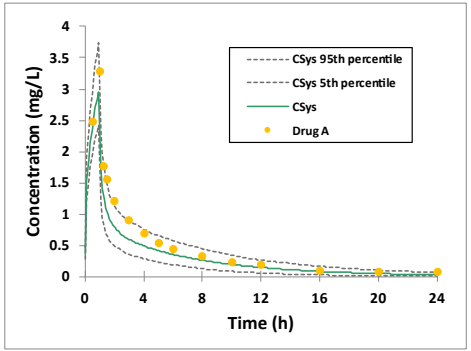
- According to the *Guidance for Industry—Control of Nitrosamine Impurities in Human Drugs (September 2024),* for BCS IV immediate-release (IR) drug products, due to their low solubility, low permeability, and associated complexity on BE assessment, the alternative approaches laid out for BCS Class I, II, and III IR products (e.g., comparative dissolution testing) are deemed not appropriate for BA or BE establishment.
- However, the guidance indicates that well-established and sufficiently validated physiologically based pharmacokinetic (PBPK) models can support BA/BE demonstration following formulation changes for nitrosamine-impacted **BCS IV oral drug products**, which can potentially support biowaiver justification.
- FDA Internal Research: PBPK absorption models were developed to predict the impact of excipient-induced changes in permeability and dissolution on PK profiles and BE outcomes for reformulated nitrosamine-impacted BCS IV oral IR drug products.

Case Example 3: PBPK absorption models to support BE assessment for reformulated nitrosamine-impacted BCS IV oral IR drug products- Background

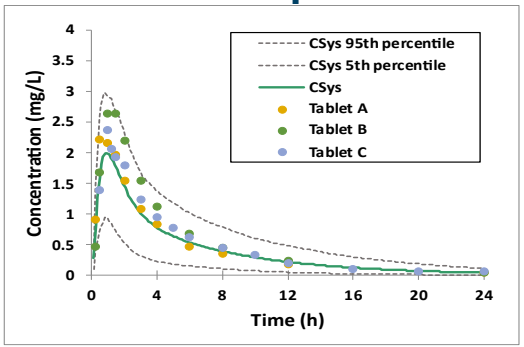
Drug A is an antibiotic classified as BCS IV (low solubility, moderate-high permeability).

- **Absorption:** Exhibits moderate to high permeability with an **absolute bioavailability of 60-80%** with no substantial loss by first pass metabolism.
- **Food effect:** Food slightly reduces and delays the rate of absorption (decreased Cmax, delayed Tmax) but does not significantly affect the extent of absorption (AUC).

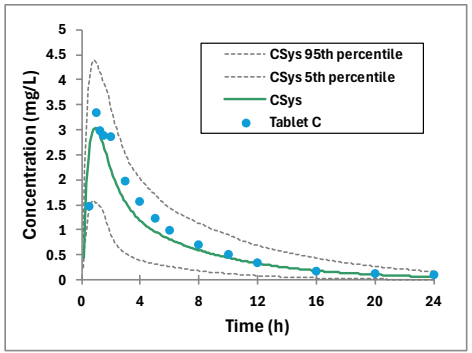
PBPK model Development



300 mg IV Infusion



500 mg Oral Tablets

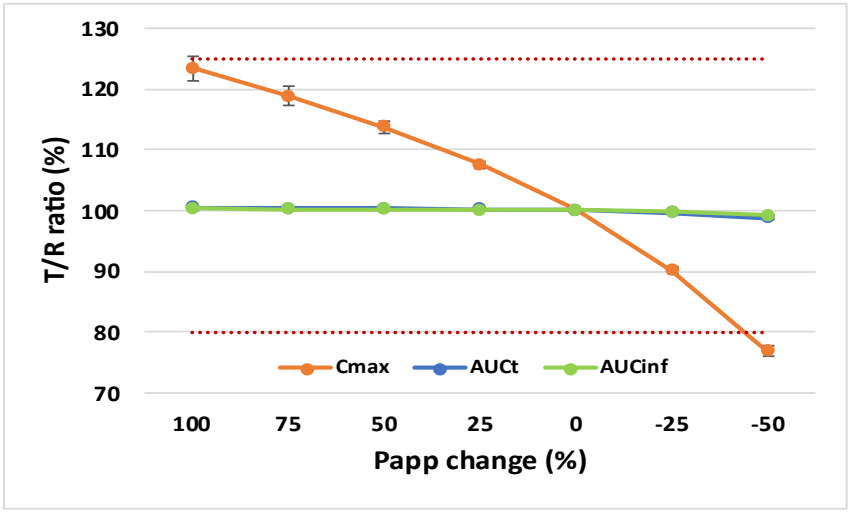


750 mg Oral Tablets

Adopted from Yi-Hsien Cheng Presentation 2026 May CRCG workshop

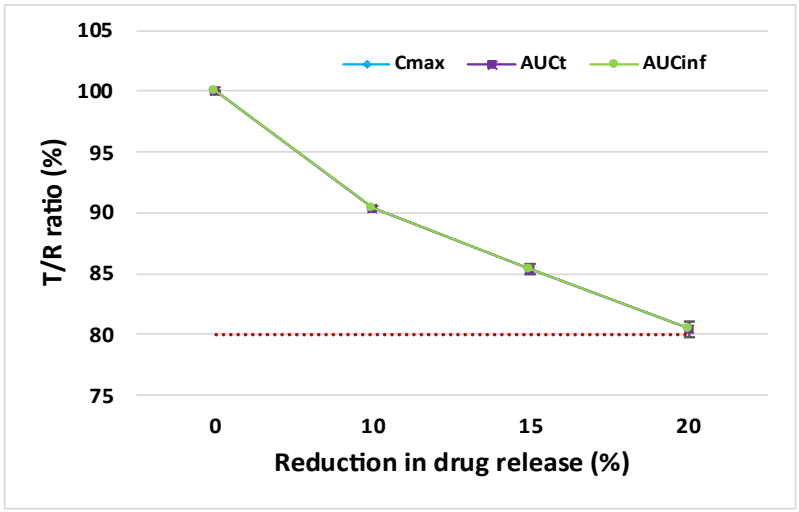
Impact of permeability change and drug release on BE for Drug A (500 mg tablet)

10 trials x 30 male/female subjects; 20-45 yrs



- Permeability changes substantially affect the rate of absorption (Cmax) but minimally impact the extent of absorption (AUCt and AUCinf) for Drug A.
- Up to 100% increase or 50% decrease in Peff will potentially cause BE failure for Cmax, but not for AUCt or AUCinf.

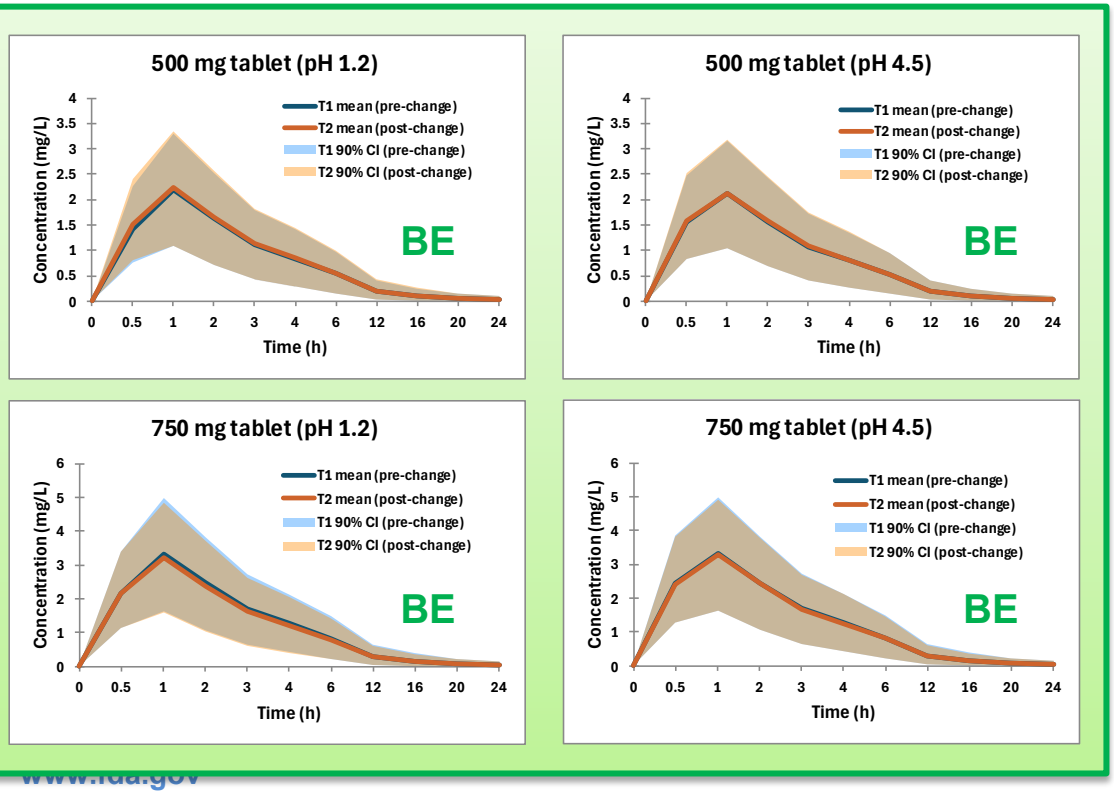
10 trials x 30 male/female subjects; 20-45 yrs



- Reduced drug release significantly impacts exposure of Drug A as indicated by both Cmax and AUC. Dissolution changes >15-20% may compromise BE.
- Dissolution testing conducted in biorelevant media can help characterize the reformulation risk for nitrosamine-impacted BCS IV drug products.

VBE for Drug A (500 and 750 mg tablets; post-change vs. pre-change dissolution data)

Clinically relevant dissolution testing



Recommended next step:

Conduct VBE simulations between post-change formulation vs. RLD using their respective dissolution data in the biorelevant media (if available)

Case 3 Summary

- PBPK modeling and sensitivity analysis indicated that dissolution testing in biorelevant media is crucial for assessing reformulation risk for Drug A product.
- For solubility-limited BCS II-like BCS IV IR products, sufficiently validated PBPK model that incorporates comparative dissolution testing in biorelevant media may potentially provide scientific justification and support biowaiver.
- PBPK modeling framework, together with the quantitative biopharmaceutics information, can be used to support risk assessment and BE demonstration following reformulation for Drug A and subsequently applied to other BCS IV drugs.

Case Example 4: PBPK Supports Development of PSG for Cladribine Tablets

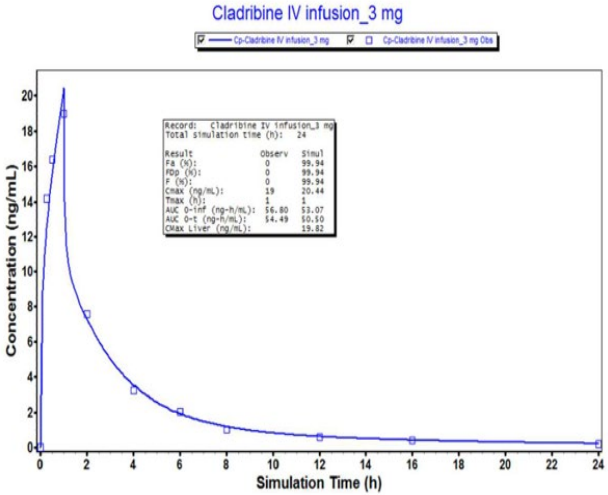
Background

- Drug: Cladribine tablets (Mavenclad 10 mg) — classified BCS III (EMA).
- Challenge: Drug substance degrades in acidic environments (in vitro).
- Per Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021).
  - >10% degradation → solubility cannot be adequately determined.
  - Significant degradation precludes BCS high-permeability classification.
  - BCS-based biowaiver eligibility is therefore uncertain.

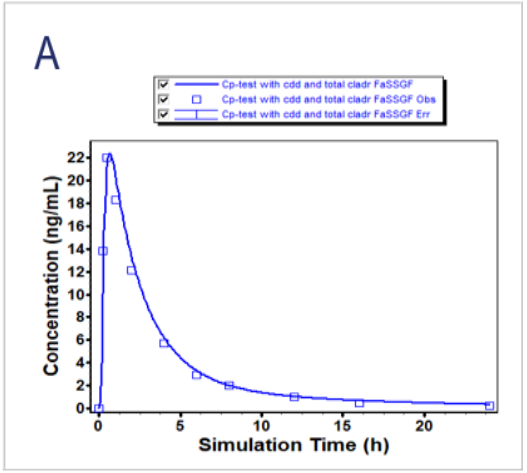
Risk Assessment Approach

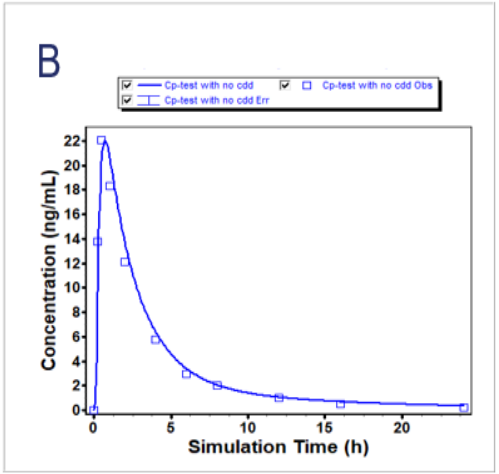
- Literature evidence from in vivo studies assessing the impact of gastric pH change (i.e., PPI coadministration) on the rate and extent of absorption of cladribine.
- Comparison of cladribine degradation (extent and rate) between generic cladribine 10 mg tablet and Mavenclad 10 mg tablet across the physiologically relevant acidic pH range.
- PBPK modeling to assess the impact of drug degradation on in vivo performance of the drug product.

Development of Cladribine PBPK Disposition and Absorption Model



Intravenous (IV) infusion of cladribine (3 mg)



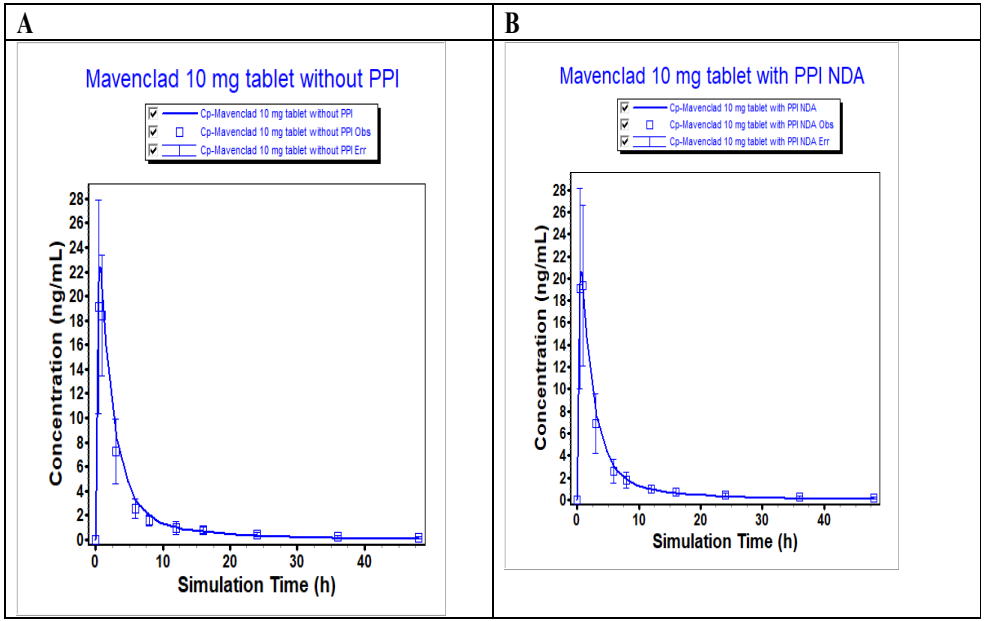


- A) Degradation data as model input to account for cladribine degradation in the model was needed when total cladribine In vitro dissolution (IVD) data in Fasted State Simulated Gastric Fluid (FaSSGF) media were used as model inputs. B) Using cladribine only IVD data in FaSSGF media as input without degradation data also predicted well
- **IVD data using FaSSGF medium is biopredictive for fasted conditions**

IV and oral data from literature (Hermann R et al. The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. Clinical Pharmacokinetics (2019) 58:283–297)

Model Validation- with or without PPI

- The model replicated the results from in vivo findings that evaluated the differences between cladribine PK profile without and with PPI.
- Degradation at lower pH does not have significant impact on PK for both RLD and test products as evidenced by the similar PK in the absence and presence of PPI.

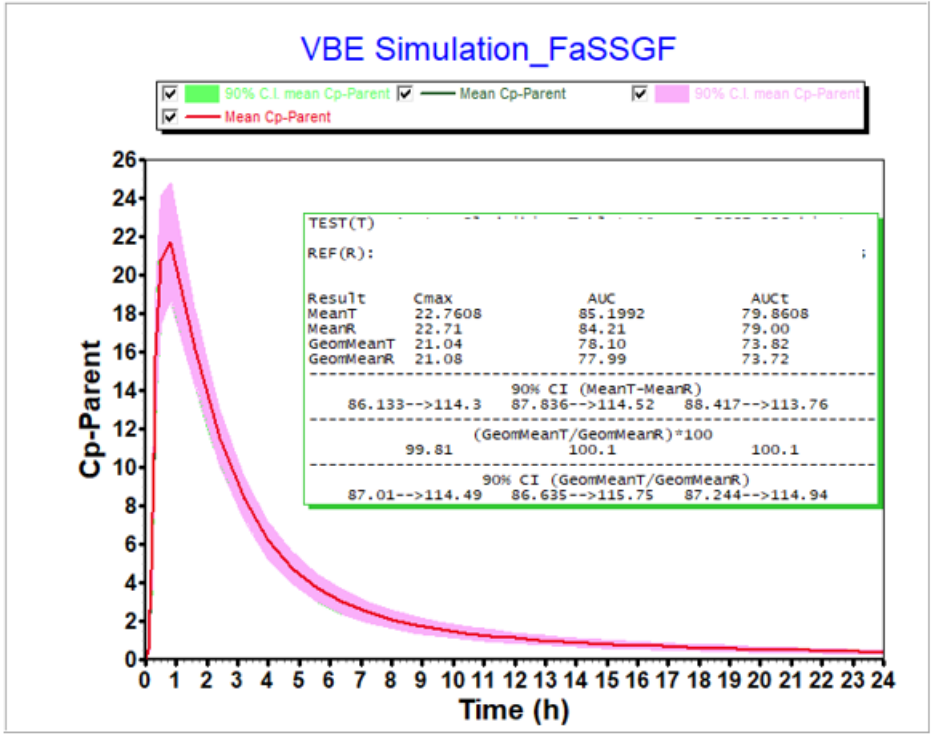


Observed PK data was obtained from reference: Hermann R et al. The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. Clinical Pharmacokinetics (2019) 58:283–297.

PPI: proton pump inhibitor

Model Application: VBE Using Dissolution in FaSSGF Medium

- VBE simulation was conducted comparing RLD and test cladribine 10 mg tablets under fasting conditions.
- The simulation demonstrated BE for RLD and test cladribine 10 mg tablets using degradation data (%degradation/hr at acidic condition) and biopredictive total cladribine dissolution data (in FaSSGF media). The impact of degradation is similar on RLD and test product.



Case 4 Summary

- A PBPK model was developed to assess the impact of cladribine degradation under acidic conditions on BE by incorporating biopredictive dissolution data as direct model input.
- The model was able to predict the result from in vivo BA study that evaluated the impact of gastric pH changes on cladribine PK after the administration of PPI (i.e., pantoprazole).
- This model was then used to demonstrate that cladribine degradation in acidic conditions with similar rate between generic product and RLD does not impact BE of generic cladribine 10 mg tablet to RLD.
- PSG for cladribine oral tablets was updated to include a BCS Class III-based biowaiver option.

Revised PSG for Cladribine Tablet. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022561.pdf

Conclusion

- PBPK modeling regulatory research projects were conducted to support the development of ICH M13A general guidance in terms of providing justifications for waiving unnecessary in vivo BE study.
- PBPK modeling regulatory research projects provided proof of concept to support nitrosamine guidance for risk assessment and BE demonstration following reformulation for BCS IV IR drug products.
- PBPK support revising the PSG for cladribine oral tablets with degradation at acidic conditions to include a BCS Class III-based biowaiver option.
- PBPK modeling is continuing to support the development and implementation of general and product specific guidance.

Acknowledgments

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