Session 2

Novel Bioequivalence Study Design Recommendations

Session Leads: Angelique Besold, PhD & Andrew Babiskin, PhD

CDR Yi Zhang, PhD
Senior Scientific Advisor
DTPII | ORS | OGD | CDER | FDA

Usha Katragadda, PhD
Senior Pharmacologist
DBIII | OB | OGD | CDER | FDA

Fang Wu, PhD
Senior Pharmacologist
DQMM | ORS | OGD | CDER | FDA

Min Tzu Chung, PharmD
Pharmacokineticist
DBIII | OB | OGD | CDER | FDA

Deniz Ozdin, PhD
Pharmacologist
DQMM | ORS | OGD | CDER | FDA

Karen Li, PharmD
Pharmacologist
DTPII | ORS | OGD | CDER | FDA

Duyen Nguyen, PharmD
Pharmacologist
DTPII | ORS | OGD | CDER | FDA

Yuqing Gong, PhD
Senior Pharmacologist
DQMM | ORS | OGD | CDER | FDA

Biopharmaceutics Classification System Waiver Option in Product-Specific Guidances

Yi Zhang, Ph.D.
Commander, U.S. Public Health Service
Division of Therapeutic Performance II
Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

Advancing Generic Drug Development Workshop: Translating Science to Approval
Session 2: Novel Bioequivalence Study Design Recommendations
October 7, 2025

Disclaimer

This presentation reflects my own views and should not be construed to represent FDA's views or policies

Objectives

- Describe the current FDA’s standard practice, regulatory process and scientific framework in recommending Biopharmaceutics Classification System (BCS)-based biowaiver as an alternative bioequivalence (BE) approach within product-specific guidances (PSGs)
- Present FDA's initiatives, regulatory efforts and research outcomes to promote and advance BCS-based biowaiver options in generic drug development and approval

M9 Guidance Foundation for BCS-based Biowaiver

FDA Guidance for Industry:

M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021 ICH)

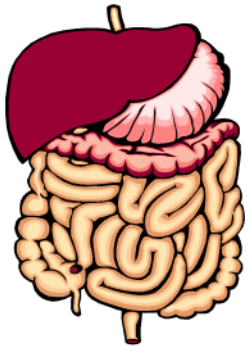
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m9-biopharmaceutics-classification-system-based-biowaivers

Scientific Foundation of BCS-based Biowaiver

A scientific framework for classifying drug substances based on

Aqueous Solubility

Intestinal Permeability



BCS Classification Criteria*

Classification	High Permeability (≥85%)	Low Permeability (<85%)
High Solubility	I	III
Low Solubility	II	IV

Note 1: High solubility-The highest single therapeutic dose is completely soluble in 250 milliliter (mL) or less of aqueous media over the pH range of 1.2–6.8 at 37±1℃.

Note 2: High permeability can be concluded:

- when the absolute bioavailability is ≥85% or
- If ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites
- Significant degradation (>10%) of a drug precludes BCS high permeability classification.

*FDA Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021 ICH) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m9-biopharmaceutics-classification-system-based-biowaivers

Benefits of BCS-based Biowaiver

- BCS-based biowaiver **is** a less burdensome alternative BE approach for immediate release (IR) solid oral drug products
  - To reduce both the costs and unnecessary human drug exposure for developing generic drugs
  - To facilitate the generic oncology drug development by alleviating the need to conduct BE studies in patients (commonly with the difficulties in patient recruitment) or healthy subjects which may pose potential safety concerns
  - To expedite the process to promote generic drug development and approval for complex drug products by avoiding the challenges in conducting comparative clinical endpoint BE studies as well as the accurate measurement of PK in vivo

Current PSG Implementation Status BCS-based Biowaiver Option

- When does a PSG recommend the BCS-based biowaiver option?
  - In general, PSG includes a BCS-based biowaiver recommendation after the Agency has determined the drug as either BCS I or III
  - As of October 2025, the BCS-based biowaiver option has been recommended in PSGs for
    - **59** BCS Class I Drugs
    - **10** BCS Class III Drugs

A Recent PSG Example (1)

Active Ingredient: Hydroxyurea

Dosage Form: Tablet

Route: Oral

Strengths: 100 mg, 1 gm

Recommended Study: Two options: (1) Biopharmaceutics Classification System (BCS)-based biowaiver or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

Option 1: BCS Class I-based biowaiver

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution of the test product and reference listed drug (RLD) as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers* is submitted in the application. Applicants may use information contained in the approved labeling of the RLD. Peer-reviewed articles may not contain the necessary details of the testing for the FDA to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request will be made upon assessment of the data submitted in the application.

Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

Recommended Nov 2022; Revised Oct 2025
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208843.pdf

A Recent PSG Example (2)

Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1 gm
Subjects: Adult male and non-pregnant and non-lactating female patients with sickle cell anemia with recurrent painful crises who are on stable regimens of hydroxyurea

Additional comments: Exclude patients who require dosage modification or with expected changes in concomitant medications that may potentially affect the pharmacokinetics of hydroxyurea during the study. Females of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for at least 6 months after the last dose. Implement safety precautions and monitoring including complete blood count during treatment as recommended in the labeling. Submission of an investigational new drug application is required prior to the conduct of a bioequivalence study for a cytotoxic drug such as hydroxyurea pursuant to 21 CFR § 320.31.

Analyte to measure: Hydroxyurea in plasma

Bioequivalence based on (90% CI): Hydroxyurea

Waiver request of in vivo testing: 100 mg strength based on (i) an acceptable bioequivalence study on the 1 gm strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Recommended Nov 2022; Revised Oct 2025
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208843.pdf

PSG for an Oncology Drug-Capecitabine Tablets

Recommended studies:

Two Options: BCS I-based Biowaiver or In Vivo BE Study with Pharmacokinetic Endpoints

Option 1: BCS I-based biowaiver

A waiver for this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution, as detailed in ICH M9 Guidance.

Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

Type of study: Fed
Design: Single-dose, two-way, crossover in vivo
Strength: 500 mg
Subjects: Cancer patients already receiving a stable twice-daily dosing regimen as prescribed by the reference product label
Additional Comments: Submission of a Bio Investigational New Drug Application (BioIND) is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as capecitabine (see 21CFR § 320.31).

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Capecitabine_Tabs_20896_RC09-12.pdf

Note: There is one ANDA approved for this drug product via BCS I-based biowaiver.

PSG for Pentosan Polysulfate Sodium Capsules

Complex Active Pharmaceutical Ingredients

Recommended studies:

Two Options: BCS III-based Biowaiver or In Vivo BE Study with Clinical Endpoints

Option 1: BCS III-based biowaiver

A waiver for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution, and the test product formulation is qualitatively the same and quantitatively very similar as detailed in ICH M9 Guidance.

Option 2: One comparative BE study with clinical endpoints

Type of study: Bioequivalence study with a clinical endpoint

Design: Randomized, double blind, parallel, placebo-controlled

Strength: 100 mg

Subjects: Male and female patients with bladder pain associated with interstitial cystitis

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020193.pdf

BCS-based Biowaiver PSGs

- ***Question:*** Is the BCS-based biowaiver a possible BE approach even it is not recommended in the PSG?
- ***Answer:*** **YES!** There are hundreds of drugs that could be eligible for BCS I or III!
  - PSGs currently represent the conclusion of FDA assessment
  - You may be the first applicant to consider a BCS-based biowaiver option to support a specific generic drug approval

PSG Example of BCS III Drug

Rasagiline Mesylate Tablets

Recommended studies:

Two Options: BCS III-based Biowaiver or In Vivo BE Study with Pharmacokinetic Endpoints

Option 1: BCS III-based biowaiver

A waiver for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution, and the test product formulation is qualitatively the same and quantitatively very similar as detailed in ICH M9 Guidance.

Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 1 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021641.pdf

Note: There are ANDAs approved for this drug product via BCS III-based biowaiver.

Identification Strategy for BCS-based Biowaiver Candidates

- ***Question:*** What IR drug products might be potential candidates for BCS-based biowaiver even when the PSG does not recommend it as an option?
- ***Answer:*** Drugs having high solubility may be eligible.
- **Factors to consider for BCS-based biowaiver:**
  - Solubility is not difficult to measure
  - For BCS III, check your test product and the RLD for very rapid dissolution
  - For BCS III, compare your proposed formulation to the RLD
  - If it is uncertain whether it is a BCS I drug, a BCS III-based biowaiver can be requested
    - Advantage => No permeability data needed
    - Disadvantage => ***Formulation similarity*** and ***very rapid dissolution*** needed

How to Request BCS-based Biowaiver

- Submit controlled correspondence to the Agency
  - **Don't:** ask if your proposed formulation is Qualitatively (Q1) the same/Quantitatively (Q2) very similar to the reference listed drug
  - **Do:** request if your proposed product is eligible for BCS-based biowaiver with supporting information
- May submit pre-ANDA meeting request for BCS-based biowaiver with supporting information
- Submit ANDA for BCS-based biowaiver with appropriate supportive data regarding high solubility and high permeability for BCS I drugs, high solubility, low permeability, very rapid dissolution, and Q1 the same and Q2 similar formulation to the reference listed drug for BCS III drugs.

Scientific Justification Approach

- What can you provide for the totality of evidence to justify acceptance of drug substance degradation exceeding 10% as per M9 Guidance?
  - **Cladribine Tablet** PSG recommends BCS III-based biowaiver option https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022561.pdf
    - Used the PBPK Modelling to justify the eligibility of BCS III-based biowaiver for Cladribine Tablet which has a greater than 10% degradation of cladribine (More details in the next presentation of this session: ***Addressing Degradation Challenges in BCS Class III Biowaiver Applications Through Physiologically Based Pharmacokinetic (PBPK) Modeling*** **by Drs. Katragadda and Wu**

FDA Research on Formulation Flexibility for BCS III-based Biowaiver

- Deviations from the criteria of Q1 the same and Q2 similar formulation to the reference listed drug for the putative BCS III drugs as per M9 guidance:
  - **Research Outcome on Formulation Assessment:** *Effect of the Similarity of Formulations and Excipients of Approved Generic Drug Products on In Vivo Bioequivalence for Putative Biopharmaceutics Classification System Class III Drugs Formulation assessment:* ***Pharmaceutics 2023, 15(9), 2366***

Formulation Survey Results of Putative BCS III Drugs

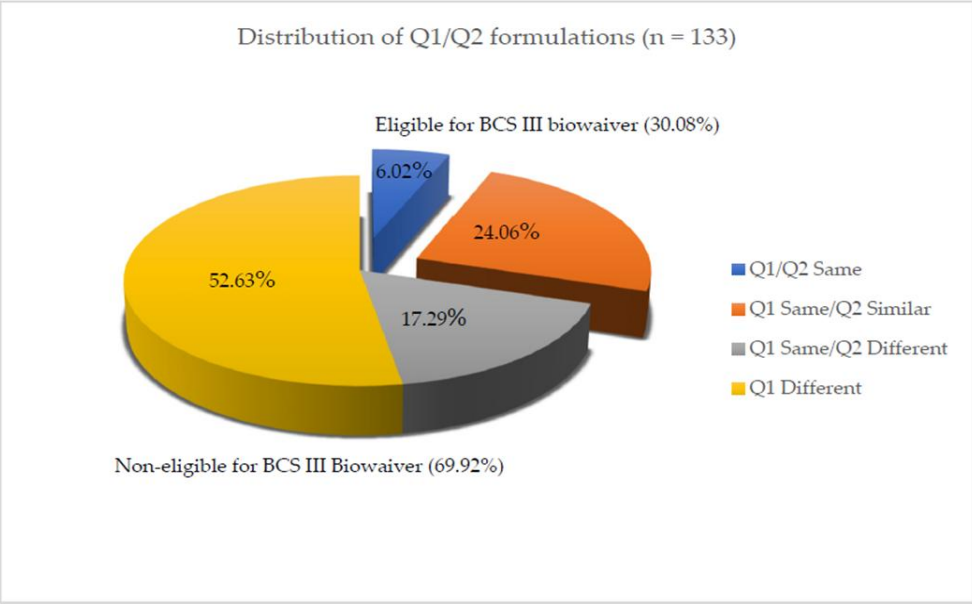


Figure 1. Distribution of diverse Q1 and Q2 formulations for in vivo BE studies. Approximately 30.08% of generic formulations were Q1/Q2 same or Q1 same/Q2 similar and 69.92% of generic drug formulations were non-Q1/Q2 similar.

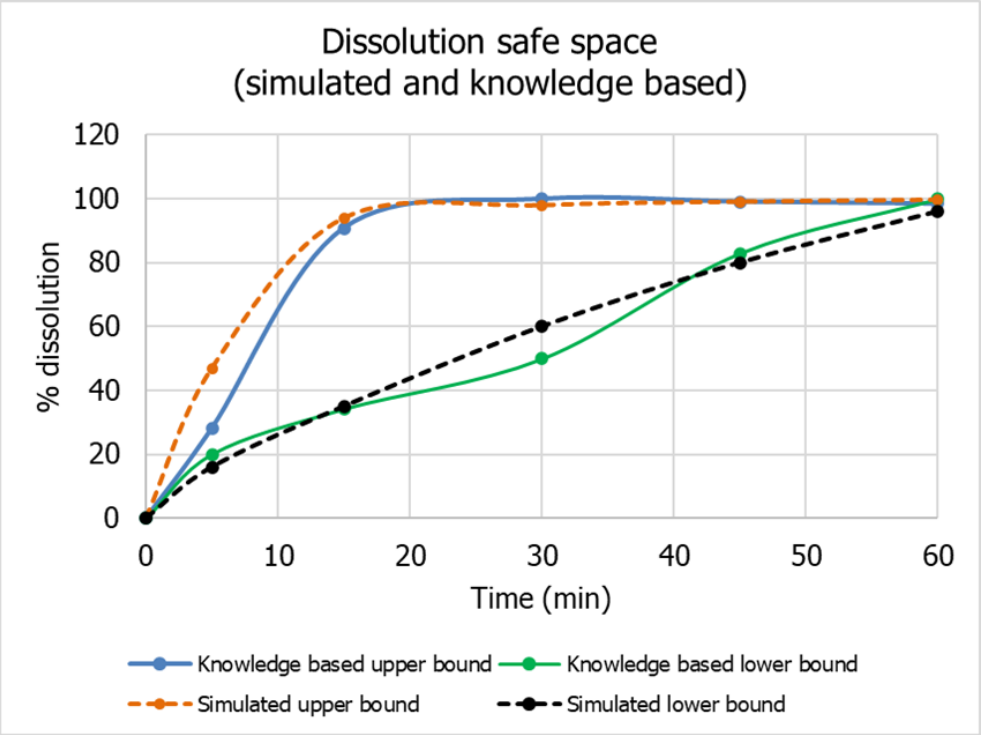
Data Source: Ren P, Chan T, Yang WC, Frost M, Wang Y, Luke M, Kim MJ, Lionberger R, Zhang Y.:Effect of the Similarity of Formulations and Excipients of Approved Generic Drug Products on In Vivo Bioequivalence for Putative Biopharmaceutics Classification System Class III Drugs – PubMed Pharmaceutics. 2023 Sep 21;15(9):2366. doi:10.3390/pharmaceutics15092366

FDA Research Findings on BCS III-based Biowaiver

- The commonly used excipients collected from 133 approved ANDAs may not affect intestinal absorption of 16 investigated putative BCS Class III drugs.
- The rate and extent of absorption of those drugs appears to be more dependent upon the biopharmaceutic and physiologic properties of BCS Class III drug substance and less, or not, dependent upon their formulations with different commonly used excipients and excipient classes.
- This study may help to explore more flexibility for BCS III-based biowaiver recommendation regarding the current formulation criteria of Q1 sameness/Q2 similarity as per M9 guidance, particularly for drug substances with moderate permeability.

FDA Research on PBPK Modeling Flexibility for Dissolution Criteria

- Potential supportive data for BCS III drug deviates from the criteria of very rapid dissolution (NLT 85% in 15 mins) as per M9 Guidance:
  - Developed and validated a Physiologically Based Pharmacokinetic (PBPK) Modelling for a putative BCS III Drug
  - Used this PBPK model to conduct Virtual BE simulations to establish BE dissolution safe space for a putative BCS III Drug



Reference: Arindom Pal, Ping Ren, Yi Zhang, Lanyan Fang, Liang Zhao, Fang Wu: PBPK Modeling to Support the Expansion of Biowaiver to Non-Q1/Q2 BCS-III Drug Products, ASCPT 2025

Summary

- **FDA Current Implementation Status:** Established comprehensive framework supporting 69 PSGs with BCS-based biowaiver options, demonstrating systematic evaluation and approval processes for generic drug applications
- **FDA Innovative Research:** Advanced scientific understanding through product risk mitigation studies and PBPK modeling approaches to support the potential expansion of BCS-based biowaiver eligibility beyond current M9 guidance criteria
- **Regulatory Innovation:** Proactively developed scientific approaches to provide BCS-based biowaiver options in PSGs, enabling faster generic drug access while maintaining solid scientific rigor

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- Lei Zhang, Ph.D.
- Robert Lionberger, Ph.D.

Questions?

Yi Zhang, Ph.D.
Commander, U.S. Public Health Service,
Division of Therapeutic Performance II,
Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

Addressing Degradation Challenges in BCS Class III Biowaiver Applications Through PBPK Modeling (Part I)

Advancing Generic Drug Development 2025:

Day (1), Session (2):

(Novel Bioequivalence Study Design Recommendations)

Usha Katragadda, Ph.D.

Senior Pharmacologist
Division of Bioequivalence III, Office of Bioequivalence
Office of Generic Drugs | CDER | U.S. FDA
October 7, 2025

Learning Objectives

- Understand Biopharmaceutics Classification System (BCS) general considerations for BCSIII biowaiver
- Evaluate bioequivalence (BE) based on the totality of evidence for case study
- Apply the role of PBPK modeling in regulatory decision making

PBPK: physiologically-based pharmacokinetics

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M9 BCS- Based Biowaivers Guidance

BCS III Based Biowaiver

Biopharmaceutics Classification of the drug substance (DS) →
- High Solubility
- Low Permeability

Eligibility of a drug product for BCS-based biowaiver →
- Formulation Similarity
- *Rapid In vitro* Dissolution Release

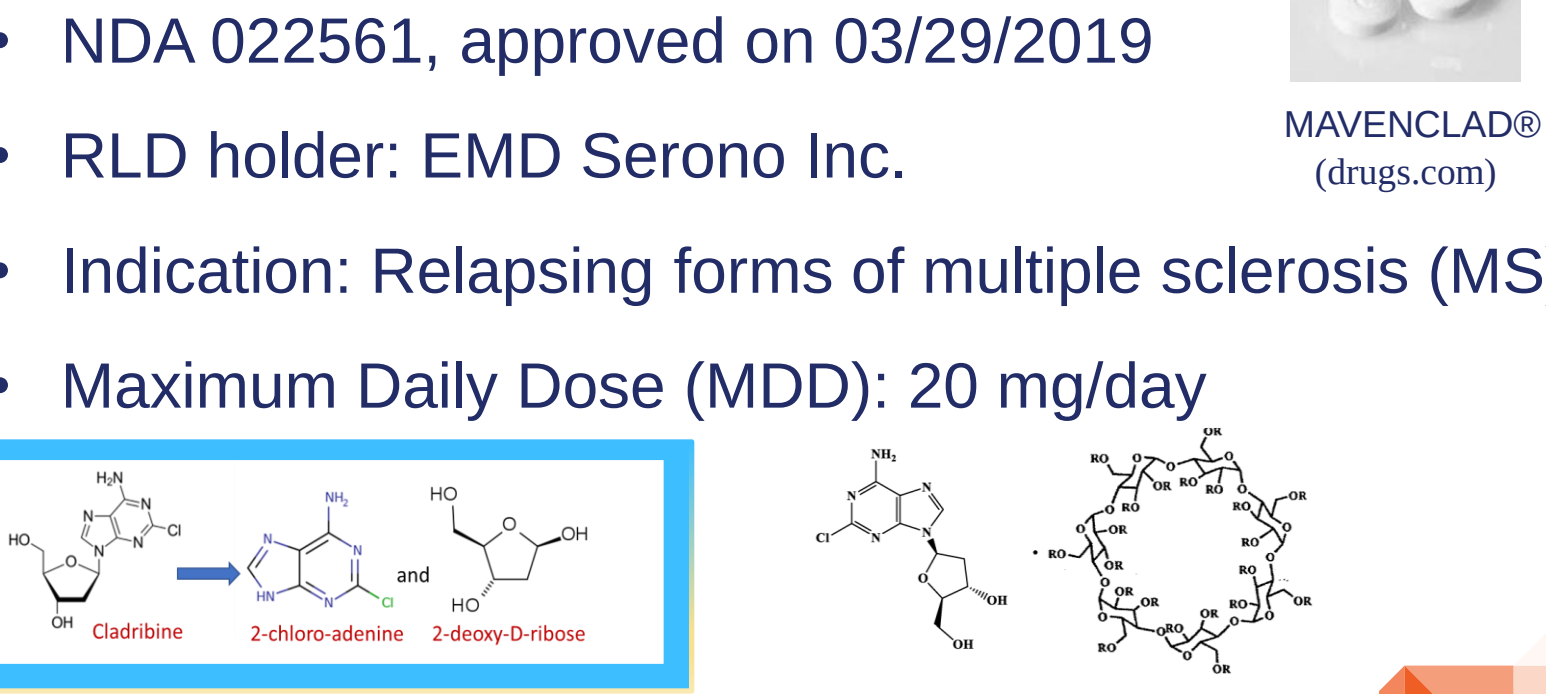
BCS III Based Biowaiver

- DS is classified as highly soluble if the highest single therapeutic dose is completely soluble in ≤ 250 ml of aqueous media over the **pH range of 1.2 – 6.8** at 37±1°C.
- Use a **validated method** to determine conc. of DS.
- Adequate stability of the DS **(≤ 10% degradation)** should be demonstrated
- Excipients qualitatively same and quantitatively similar as the reference listed drug, as defined in the M9 BCS guidance
- Very rapid dissolution (≥85% within 15 min at pH 1.2, pH 4.5 and pH 6.8)

Case Study for Tablets with Acid Instability Challenges

Reference Listed Drug (RLD)

- MAVENCLAD® (cladribine) Tablets, 10 mg
- NDA 022561, approved on 03/29/2019
- RLD holder: EMD Serono Inc.
- Indication: Relapsing forms of multiple sclerosis (MS)
- Maximum Daily Dose (MDD): 20 mg/day

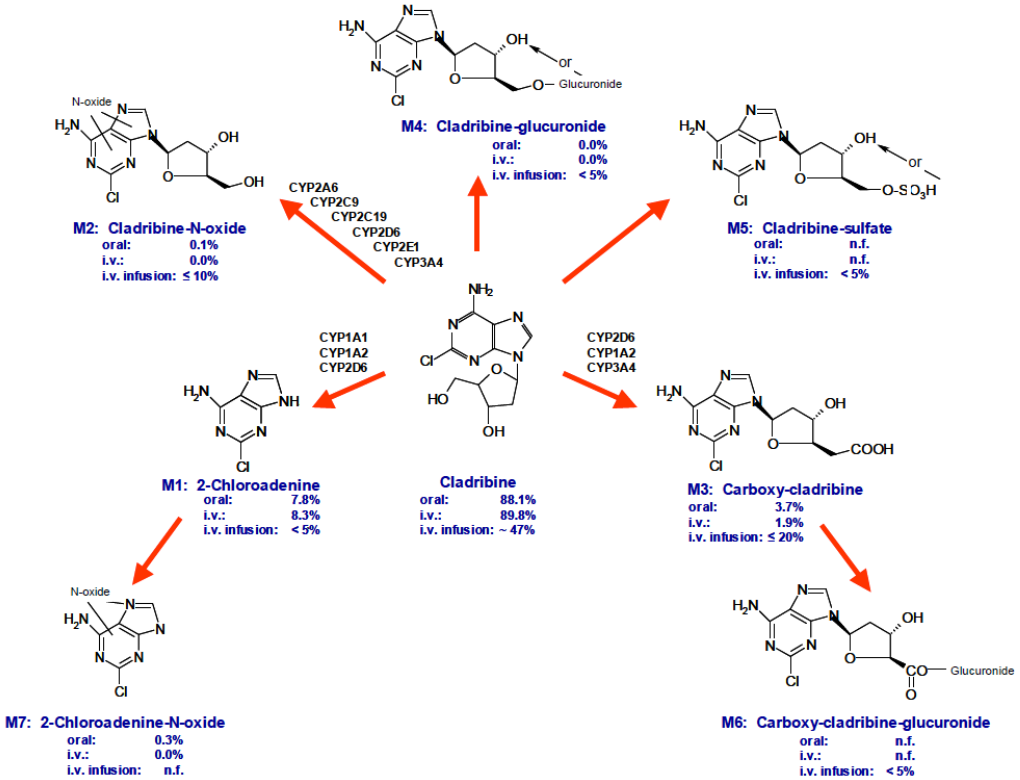


MAVENCLAD®
(drugs.com)

Cladribine: 2-HPßCD complex

Cladribine Metabolism

Proposed Metabolic Pathways of Cladribine in Humans, Percentage from Total Amount Recovered in Urine



Drugs@FDA
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/022561Orig1s000ClinPharmR.pdf

Product Specific Guidance for Cladribine Tablets

Active Ingredient:	Cladribine
Dosage Form:	Tablet
Route:	Oral
Strength:	10 mg
Recommended Studies:	Two options: (1) Biopharmaceutics Classification System (BCS) III-based biowaiver or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: BCS Class III-based biowaiver

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution,[a] and the test product formulation is qualitatively the same and quantitatively similar as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[b] is submitted in the application. A decision regarding the acceptability of the waiver request can only be made upon assessment of the data submitted in the application.

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Study design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg
   Subjects: Patients with relapsing forms of multiple sclerosis who plan to receive the first or second treatment course of cladribine

Analyte to measure: Cladribine in plasma

Bioequivalence based on (90% CI): Cladribine

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Recommended Feb 2022; Revised Aug 2024
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022561.pdf

Evaluation of the Totality of Evidence in a Case Study

Initial Challenges

M9 Guidance Recommendations for BCS III Waiver

Excipients qualitatively same and quantitatively similar (Q1/Q2) as RLD

Solubility with <10% degradation and solubility is maintained over relevant timeframes

Very rapid Dissolution (≥85% within 15 min)

Cladribine Concerns Complying with M9 Guidance

Q1/Q2 formulation similarity ✓

Solubility with >10% degradation at pH 1.1-6.8 for API and pH 1.1-1.8 for complex ✗

<85% dissolution in 0.1N HCl within 15 minutes ✗

Scientific Approach

Issues/Concerns	Reasons for feasibility of BCS waiver
API/API complex	Before absorption, cladribine separates from cyclodextrin, making the stability and solubility of both the active pharmaceutical ingredient (API) and the API-cyclodextrin complex potentially important factors.
Instability at pH 1.1 to 2	Per RLD label Coadministration of pantoprazole with Cladribine Tablets - no effect on the rate and extent of the absorption

Scientific Approach

Issues/Concerns	Reasons for feasibility of BCS waiver
Dissolution	Considering dissolution data at pH 1.6 Fasted State Stimulated Gastric Fluid (FaSSGF), in addition to data at pH 1.2, 4.5 and 6.8
Degradants	Publicly available *in vivo* data
Solubility study time frame	The Tmax range (0.5 to 1.5 hours), 2 hours may be a suitable timeframe

Solubility and Dissolution Data

Solubility at pH1.6 (FaSSGF)

- Solubility exceeds target concentration by many-fold for DS and DS-complex
- Mass balance is demonstrated for DS-complex for suitable time frame

Dissolution Medium: FaSSGF, pH 1.6

>85% dissolution for Test and Reference standard within 15 minutes

PBPK for BE Evaluation

- The impact of drug degradation on in vivo performance of the drug product is evaluated by PBPK
- Dissolution data at FaSSGF media and degradation data at multiple pH were incorporated into PBPK model
- Simulations using the optimized model showed that the degradation of cladribine at lower pH did not result in non-BE

Overall, BCS Class III-based biowaiver is feasible

Challenge Question

Based on the case study discussed, which factor was MOST critical in overcoming the >10% degradation challenge for BCS III waiver approval?

A) Adequate solubility study duration
B) PBPK modeling demonstrating no impact on bioequivalence
C) Validated stability-indicating analytical methods
D) Totality of evidence including all of the above

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- DQMM/ORS Team: Drs. Lanyan (Lucy) Fang, Fang Wu, Sherin Thomas, Arindom Pal
- Center for Drug Evaluation and Research (CDER)’s BCS Committee

Thank you!

Addressing Degradation Challenges in BCS Class III Biowaiver Applications Through PBPK Modeling (Part II)

Fang Wu, Ph.D.

Senior Pharmacologist, Scientific Lead for Oral PBPK
Division of Quantitative Methods and Modeling, Office of Research and Standards
Office of Generic Drugs | CDER | U.S. FDA

Advancing Generic Drug Development Workshop: Translating Science to Approval
Day (1), Session (2): (Novel Bioequivalence Study Design Recommendations)
(October 7, 2025)

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Learning Objectives

- Present a case study of Cladribine Tablets with acid instability challenges
- Understand OGD's BE evaluation based on the totality of evidence for the Cladribine Tablets case study
- Understand the role of PBPK modeling in regulatory decision making for the approval of Cladribine Tablet

BE: bioequivalence; PBPK: physiologically-based pharmacokinetics

PBPK Supports BCS Waiver for BCS Class III Drugs with Degradation

- Cladribine tablets is considered as BCS III drug per European Public Assessment Report: Mavenclad. European Medicines Agency; 2017
- Degradation of the drug substance in acidic environments observed in *in vitro* studies
- Per Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021). Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m9-biopharmaceutics-classification-system-based-biowaivers
  - "In cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined"
  - "Significant degradation (>10%) of a drug precludes BCS high permeability classification"
  - So, it is challenging to determine whether this product is eligible for BCS-based biowaiver

PBPK Supports BCS Waiver for BCS Class III Drugs with Degradation

Question: How was the BCS-based waiver option included in revised PSG for cladribine tablets in August 2024?

I. **Option 1: BCS Class III-based biowaiver**

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution,[a] and the test product formulation is qualitatively the same and quantitatively similar as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[b] is submitted in the application. A decision regarding the acceptability of the waiver request can only be made upon assessment of the data submitted in the application.

II. **Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints**

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

PBPK model was used to support that a BCS waiver is applicable for cladribine tablets despite degradation

Background Information Regarding Degradation

- **pH solubility data** showed significant degradation (>10%) of the drug substance in acid buffers.
- **Dissolution data**
  - Very rapid dissolution (i.e., >85% dissolved within the first 15 minutes) at pH 4.5 and pH 6.8.
  - However, at 0.1N HCl dissolved <85% of labeled amount within the first 15 minutes and decreasing amounts of the observed percent (%dissolved) were found at later time points in acidic medium (including 0.1N HCl at pH1.2 and FaSSGF medium at pH 1.6) for cladribine only (not total cladribine).

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.
- Physiologically based pharmacokinetic modeling to assess the impact of drug degradation on in vivo performance of the drug product.

Development of Cladribine PBPK Disposition Model

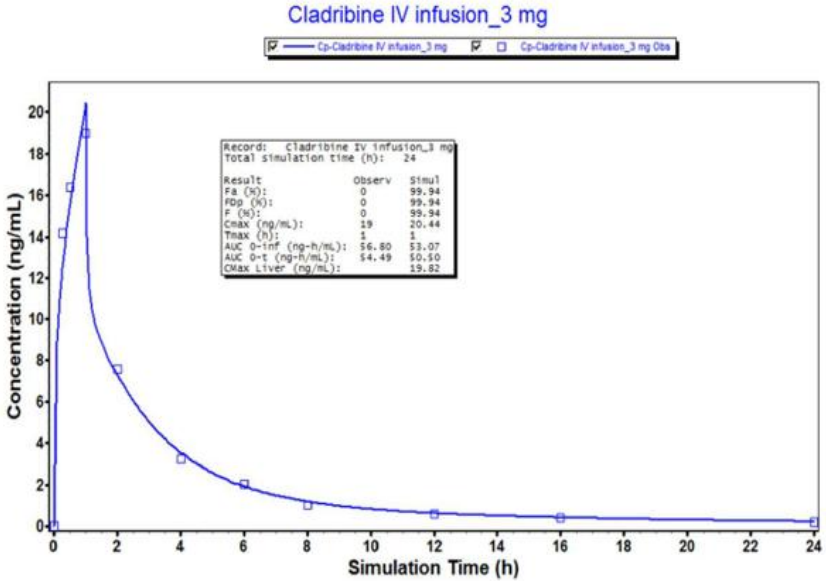
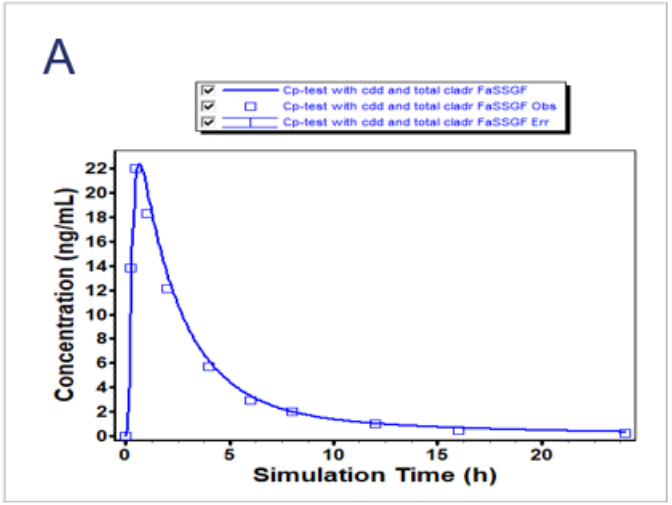
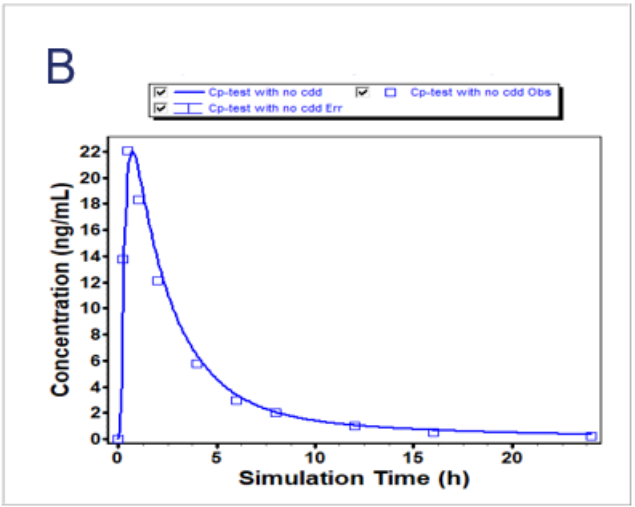


Figure. Observed vs predicted plasma concentration profile of cladribine after intravenous (IV) infusion (3 mg)

- IV 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) was used to obtain disposition parameters.

Development of Cladribine PBPK Absorption Model



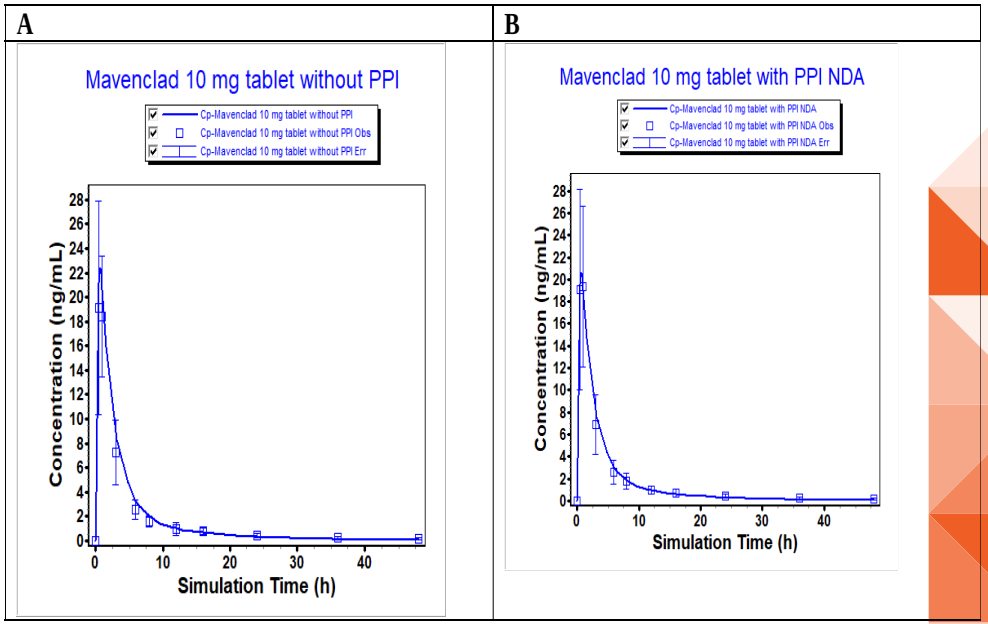


- A) Degradation data as model input to account for cladribine degradation in the model was needed when total cladribine In vitro dissolution (IVD) data in FaSSGF media were used as model inputs. B) Using cladribine only IVD data in FaSSGF media as input without degradation data also predicted well
-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

FaSSGF: Fasted State Simulated Gastric Fluid; 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.

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.

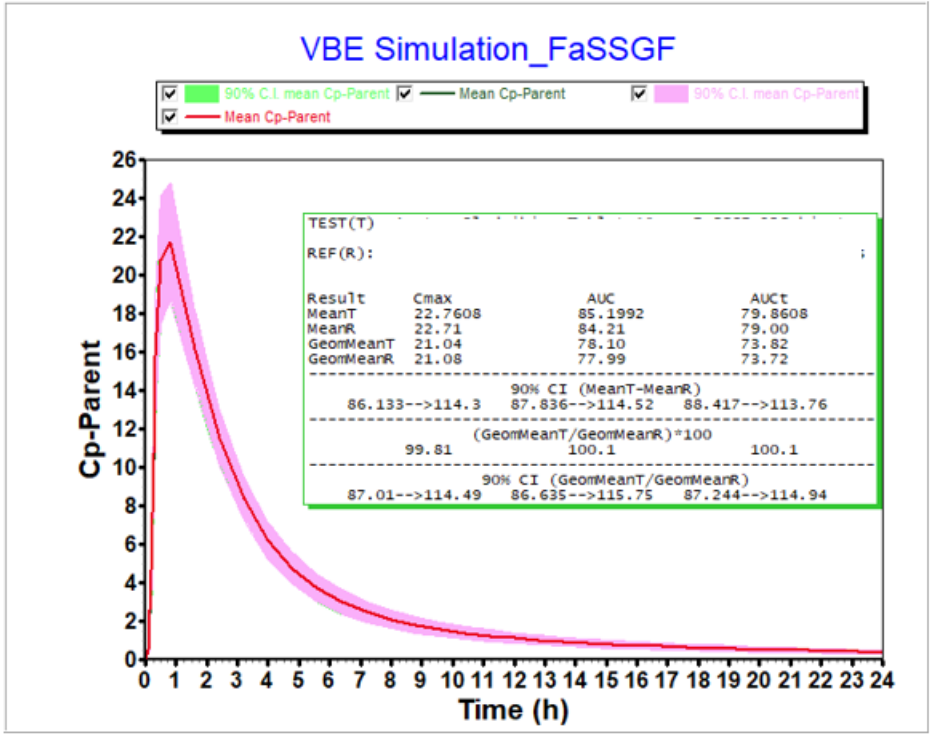


Observed PK data was obtained from reference: Hermann R et al. The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. Clinical Pharmacokinetics (2019) 58:283–297.

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.



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

Challenge Question

For cladribine case, what dissolution profiles could be incorporated into PBPK modeling to better predict the impact of cladribine degradation on BE:

A. Total cladribine in vitro dissolution data in FaSSGF media together with degradation data to account for cladribine degradation.

B. Using cladribine only in vitro dissolution data in FaSSGF media as input without degradation data

C. In vitro dissolution data using FaSSGF medium

D. All of the above

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OGD/ORS/IO

Drs. Robert Lionberger and Lei Zhang

Reviewers from Office of Bioequivalence

Drs Usha Katragadda and Moheb Makary

Questions?

Fang Wu, Ph.D.
Division of Quantitative Methods and Modeling, Office of Research and Standards
Office of Generic Drugs | CDER | U.S. FDA

(Fang.Wu@fda.hhs.gov)

Using Modeling and Simulation to Correct Carryover for Long Half-Life Drugs with Incomplete Washout

Min Tzu Chung, PharmD
Pharmacokineticist
Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
CDER | US FDA

Deniz Ozdin, Ph.D., M.Sc., BPharm
Pharmacologist
Division of Quantitative Methods and Modeling
Office of Research and Standards
Office of Generic Drugs
CDER | US FDA

Advancing Generic Drug Development Workshop: Translating Science to Approval
October 7-8, 2025
Day 1, Session 2: Novel Bioequivalence Study Design Recommendations

Disclaimer

This presentation reflects the views of the authors and should not be interpreted as the position of the United States Food and Drug Administration.

Using Modeling and Simulation to Correct Carryover for Long Half-Life Drugs with Incomplete Washout – Part 1

Min Tzu Chung, Pharm.D.

Pharmacokineticist, DBIII/OB/OGD

Learning Objectives

Part 1

- Understand current FDA recommendations on bioequivalence (BE) studies for orally administered immediate-release (IR) solid dosage forms including:
  - Long Half-life Drug Products and Carryover effects
- Discuss BE approaches in carryover effect case studies
  - New BE study required or using model-based approach for adjustment of carryover effects
  - Challenges in BE studies for long half-life drugs with carryover

Learning Objectives
Part 2

- Understand how population pharmacokinetic (Pop PK) modeling provides scientifically robust solutions to address incomplete washout scenarios
- Learn key regulatory considerations and FDA's approach to accepting alternative model-based analysis methods
- Identify opportunities to engage with FDA through model-integrated evidence (MIE) industry meeting pilot program when facing similar challenges in your drug development programs

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FDA's Recommendations on Drug Products With Long Elimination Half-lives

Long Half-life Drug Products

Elimination half-life ($t_{1/2}$)

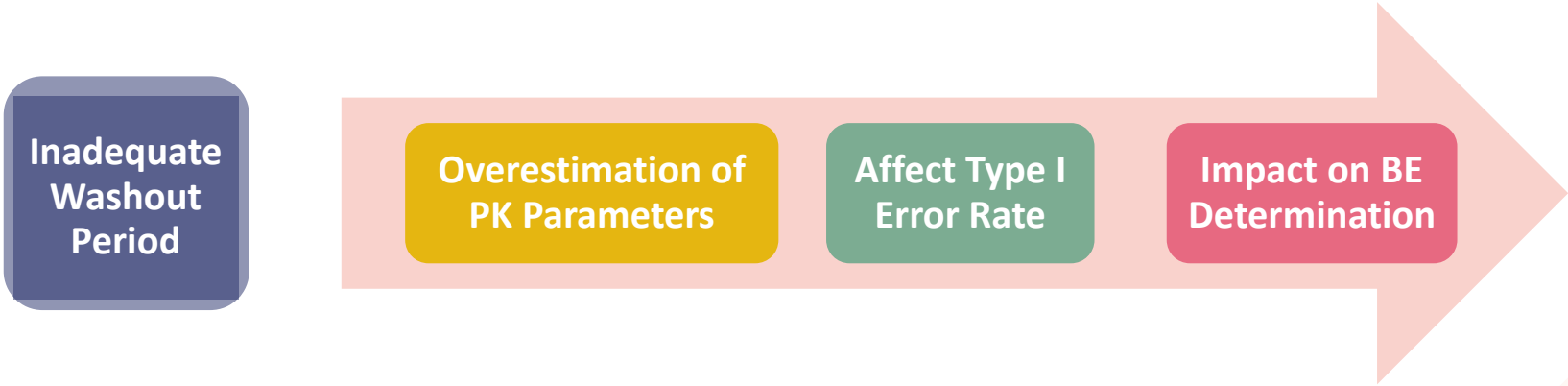
≥ 24 hours

- Reference: ICH M13A Bioequivalence for Immediate-Release (IR) Solid Oral Dosage Forms (October 2024)

- Randomized, **single-dose, crossover** design with an adequate washout period is usually recommended
  - Randomized **parallel** study design may be considered
- **Truncated AUC** may be considered in place of AUC_{0-t} for the extent of absorption comparison

Carryover Effect

Residual effects of a treatment affect participants in subsequent study periods



Recommendations from the FDA Guidance

Bioequivalence Studies with Pharmacokinetic (PK) Endpoints for Drugs Submitted Under an ANDA (Aug. 2021)

ICH M13A Bioequivalence for Immediate-Release (IR) Solid Oral Dosage Forms
(October 2024)

Adequate washout period between treatment periods

- E.g., at least **five** elimination half-lives

Pre-dose concentration evaluation

- Greater than 5% of the respective C_{max}: The subject's data for that period **should be excluded**
- Less than or equal to 5% of the respective C_{max}: **Can include the data without adjustments**

Suitable truncated AUC for long half-life

- Should cover the **complete absorption phase**
- E.g., **AUC_{0-72}**

CASE STUDIES

CARRYOVER EFFECTS

Case Study 1
(Hypothetical)

Drug Product	Oral IR Tablet
Applicant's *In Vivo* Bioequivalence (BE) Study Design	• Single-dose, two-way crossover • Washout period (≥ 5 times of reported half-lives) • Truncated AUC and C_{max}
Issue Encountered	• ~60-80% of the subjects who completed the study had pre-dose > 5% of the respective Cmax in Period 2 • Imbalance of carryover effect • Inadequate sample size

Unacceptable. **New BE study** required.

The Challenge: When Standard Bioequivalence Studies Fall Short

Prolonged Washout Period

Study timeline extended

Increase subject recruitment difficulties

Higher dropout rates

Incomplete data collection

Case Study 2

Drug Product	Oral IR Tablet
Applicant's *In Vivo* Bioequivalence (BE) Study Design	• Single-dose, two-way crossover • Washout period (> 5 times of reported half-life of the drug) • Truncated AUC and C_{max}
Issue Encountered	More than 90% of the subjects enrolled in the BE studies had pre-dose concentrations > 5% of the respective C_{max} values in Period 2

Lack of data for statistical comparison after the exclusion

Model-Based Approach

The Challenge : Impact on Study Integrity

When Carryover Occurs *Despite Extended Washout Periods*

- Period 2 data become compromised in crossover study
  - Traditional non-compartmental analysis may be insufficient
- Regulatory implications with standard approach
  - Exclude all affected subjects from analysis
  - Insufficient data for statistical comparison and BE demonstration
- May fail to demonstrate BE
  - Due to data limitations or actual product differences?
- Industry impact: Study failures, resubmissions, and development delays

Using Modeling and Simulation to Correct Carryover for Long Half-Life Drugs with Incomplete Washout – Part 2

Deniz Ozdin, Ph.D., M.Sc., BPharm

Pharmacologist, DQMM/ORS/OGD

The Solution – MIE Approach

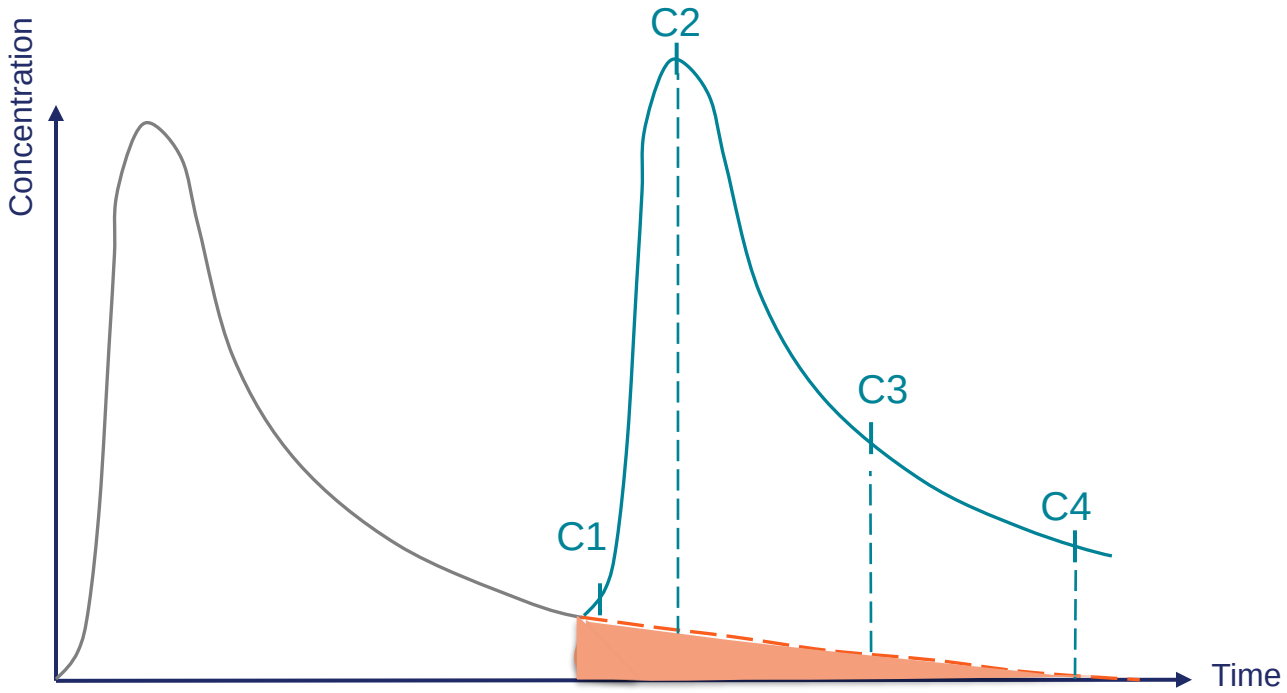
- Population PK (Pop PK) modeling provides a scientifically robust alternative to handle carryover
  - Individual-level predictions: Estimating residual drug concentrations from Period 1 for each subject
  - Precise adjustments: Removing predicted carryover effects from Period 2 observations
  - Preserved data integrity: Maintaining study data rather than excluding subjects
  - Enhanced statistical power: Enabling proper BE assessment with complete datasets

MIE: Model-Integrated Evidence

Key Advantages Over Baseline Adjustment Approach

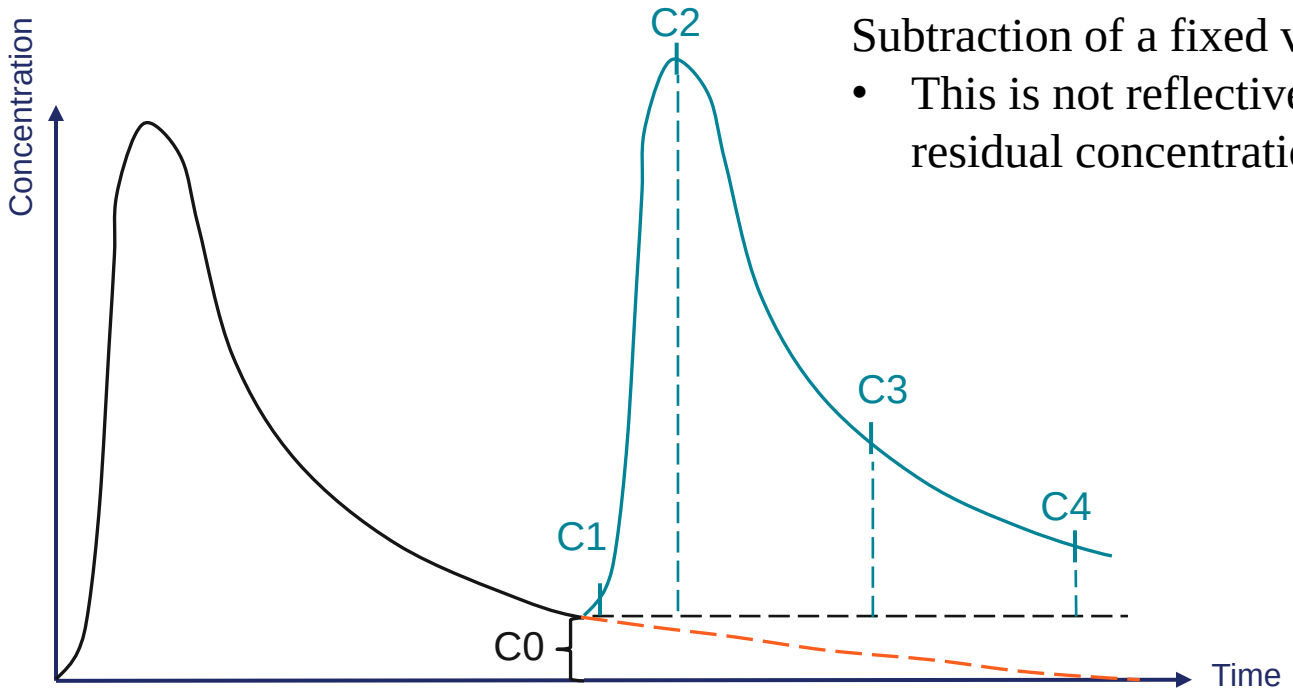
- Baseline Adjustment Approach:
  - Subtracts a fixed pre-dose value throughout Period 2
  - Limitation: Doesn't account for declining residual concentrations over time
- Pop PK Model-based Concentration Adjustment:
  - Predicts time-varying residual concentrations
  - Advantage: Reflects actual PK decline of carryover effects
  - Result: More accurate and scientifically defensible concentration corrections

Pop PK Model-Based Concentration Adjustment



IPRED-adjusted Concentrations: C1-IPRED1 C2-IPRED2 C3-IPRED3 C4-IPRED4

Baseline Adjustment Approach



Subtraction of a fixed value (C0)

- This is not reflective of decreasing residual concentration.

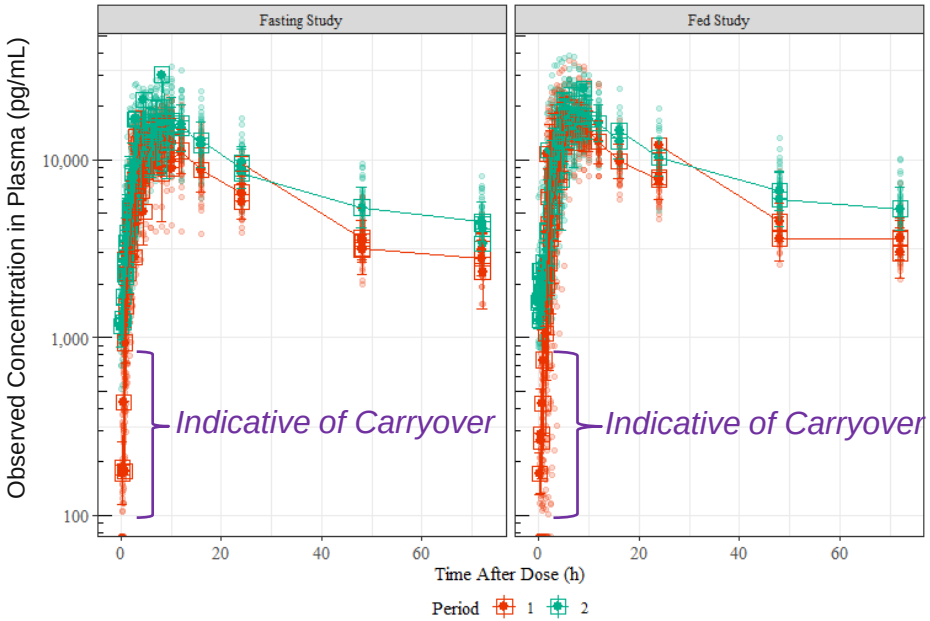
Baseline-Corrected Concentrations: C1-C0 C2-C0 C3-C0 C4-C0

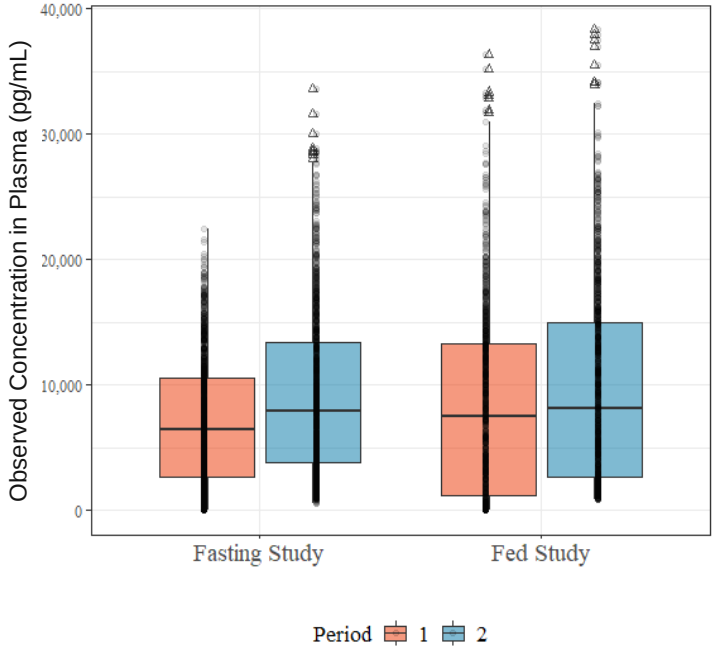
Real-World Success Story: Oral IR Tablet – Case 2 BE Studies

- **Study design:** Crossover BE studies with washout period > 7 half-lives
- **Critical problem:** Despite extensive washout, ALL subjects showed carryover effects
- **Severity:** Pre-dose concentrations in Period 2 were 6-12% of Cmax (>>5% threshold)
- FDA successfully applied Pop PK modeling to resolve carryover effects
- **Outcome:** Successful BE demonstration using IPRED-adjusted concentrations
- Providing regulatory approaches for addressing future similar challenges

IPRED : Model-predicted individual predictions

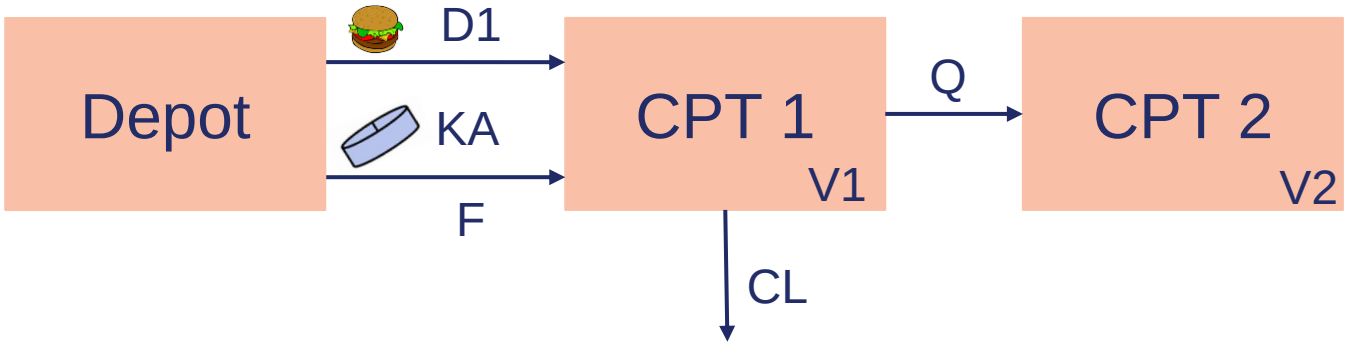
Pop PK Modeling - Data Exploration





Pop PK Modeling – Model Building

- Software: NONMEM® Version 7.5.0.
- Minimization algorithm: First-Order Conditional Estimation (FOCE)
- Sequential data pooling, e.g., fasting and fed data
- Between-subject variability (ETA)
- Covariate Analysis
  - : Food effect
  - : Treatment effect

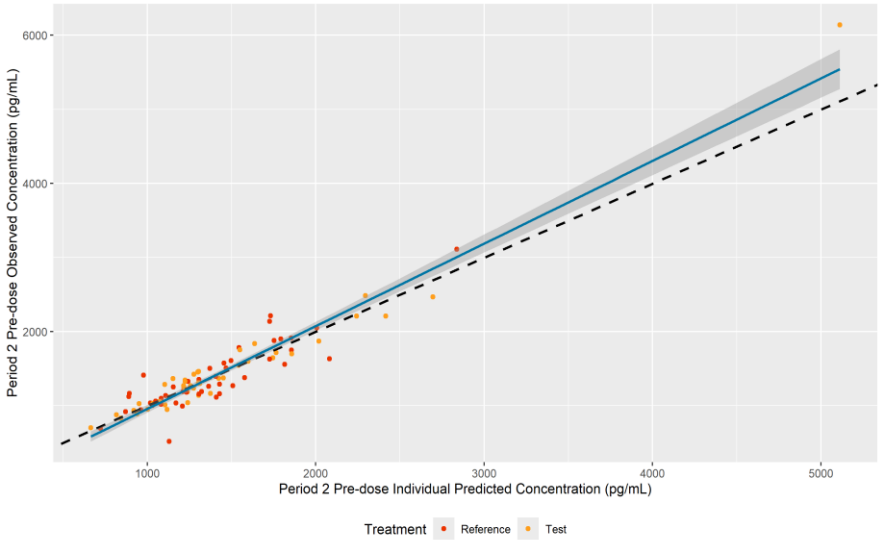


F: Apparent bioavailability (F/CL)
D1: Duration for depot CPT
CL: Clearance
Q: Intercompartmental clearance
V: Volume of Distribution
CPT: Compartment

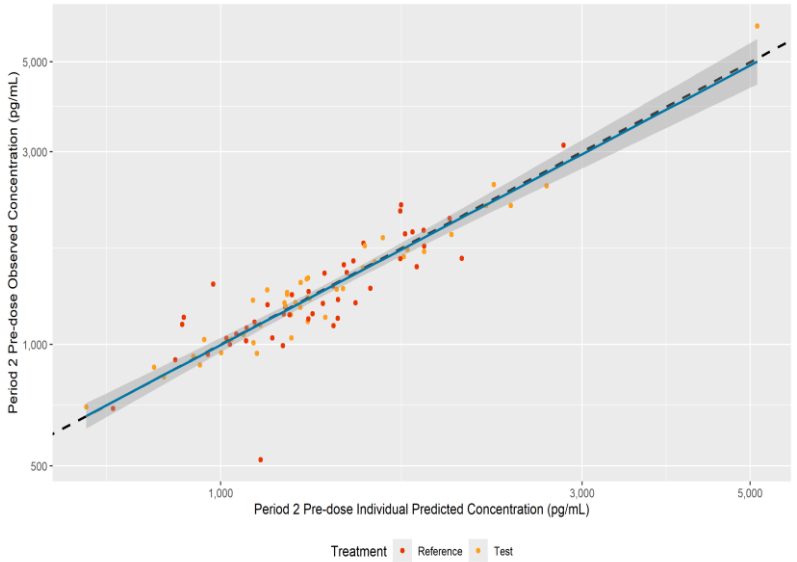
Pop PK Modeling – Model Diagnostics

Goodness-of-Fit (GOF) - Period 2 Pre-dose Timepoint

Normal scale



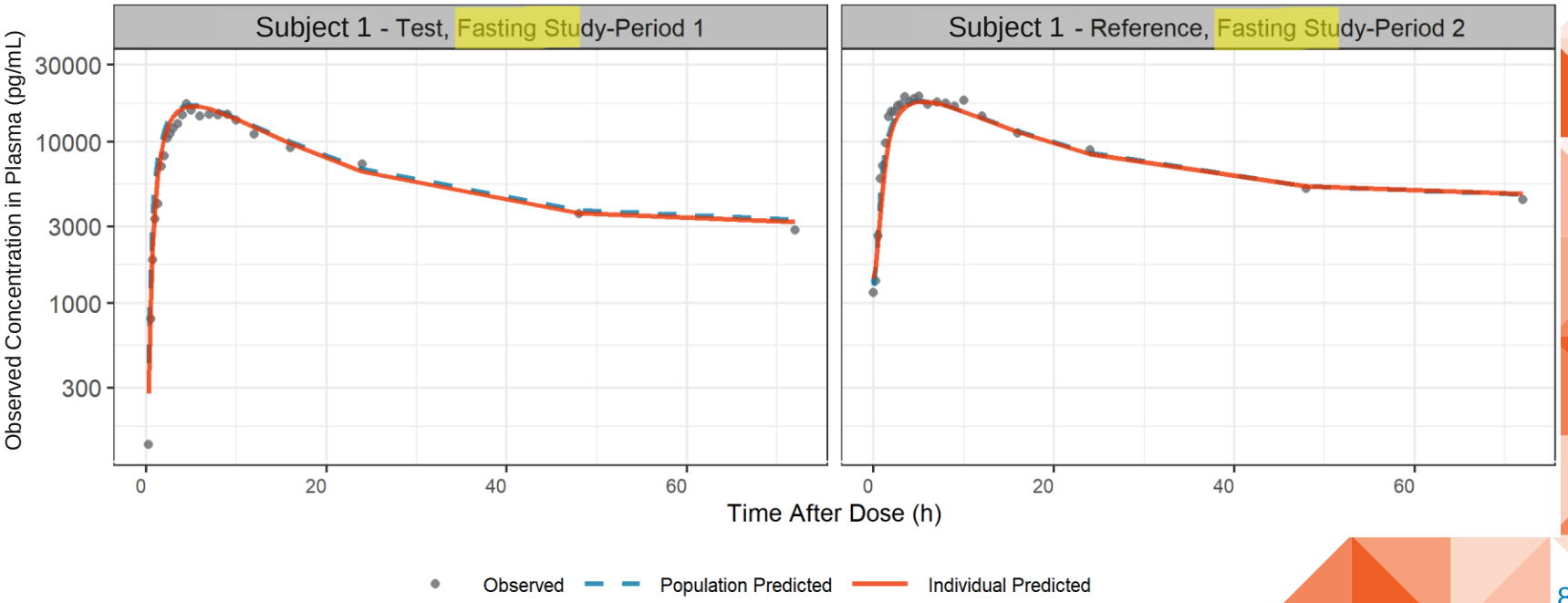
Log scale



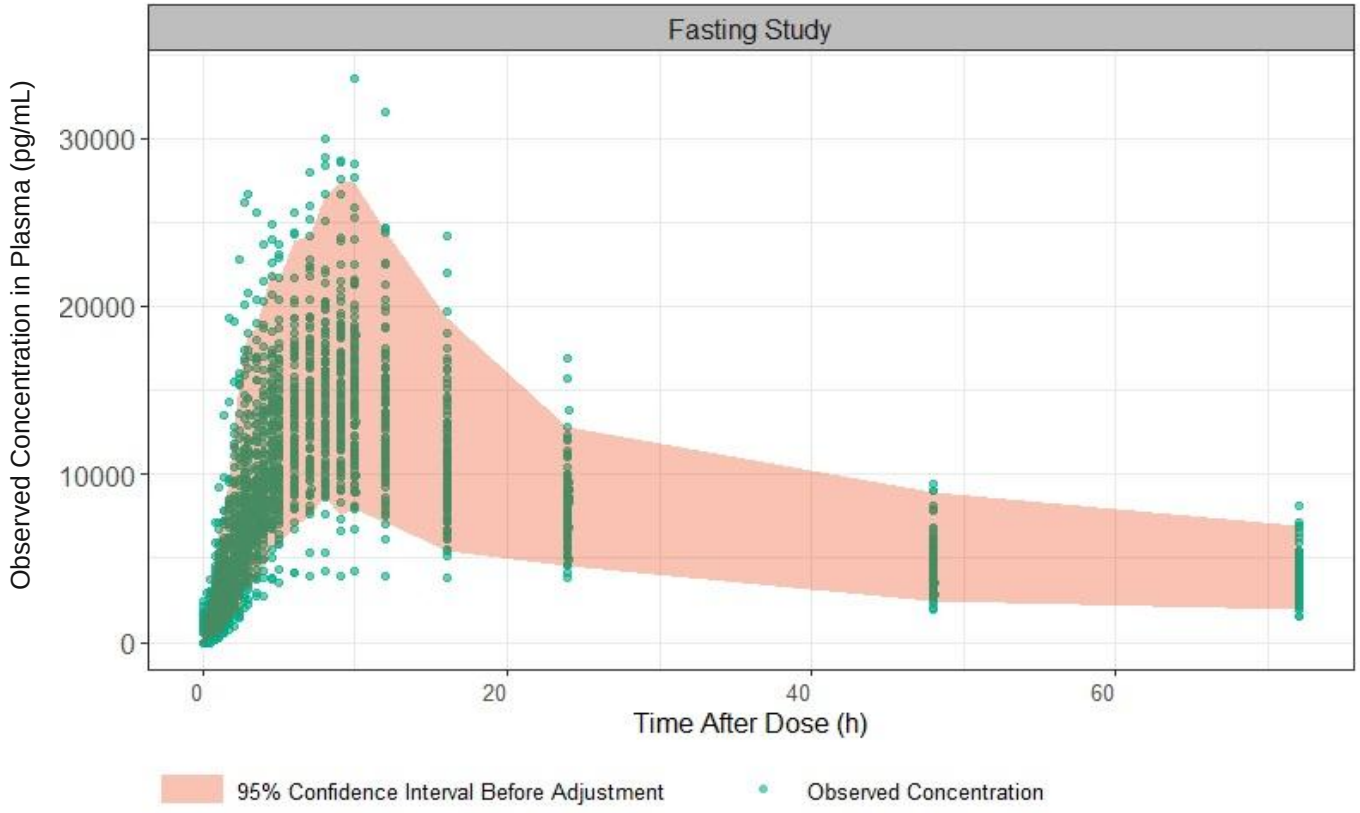
Pop PK Modeling – Model Diagnostics

Goodness-of-Fit (GOF) - Per Individual – Log Scale

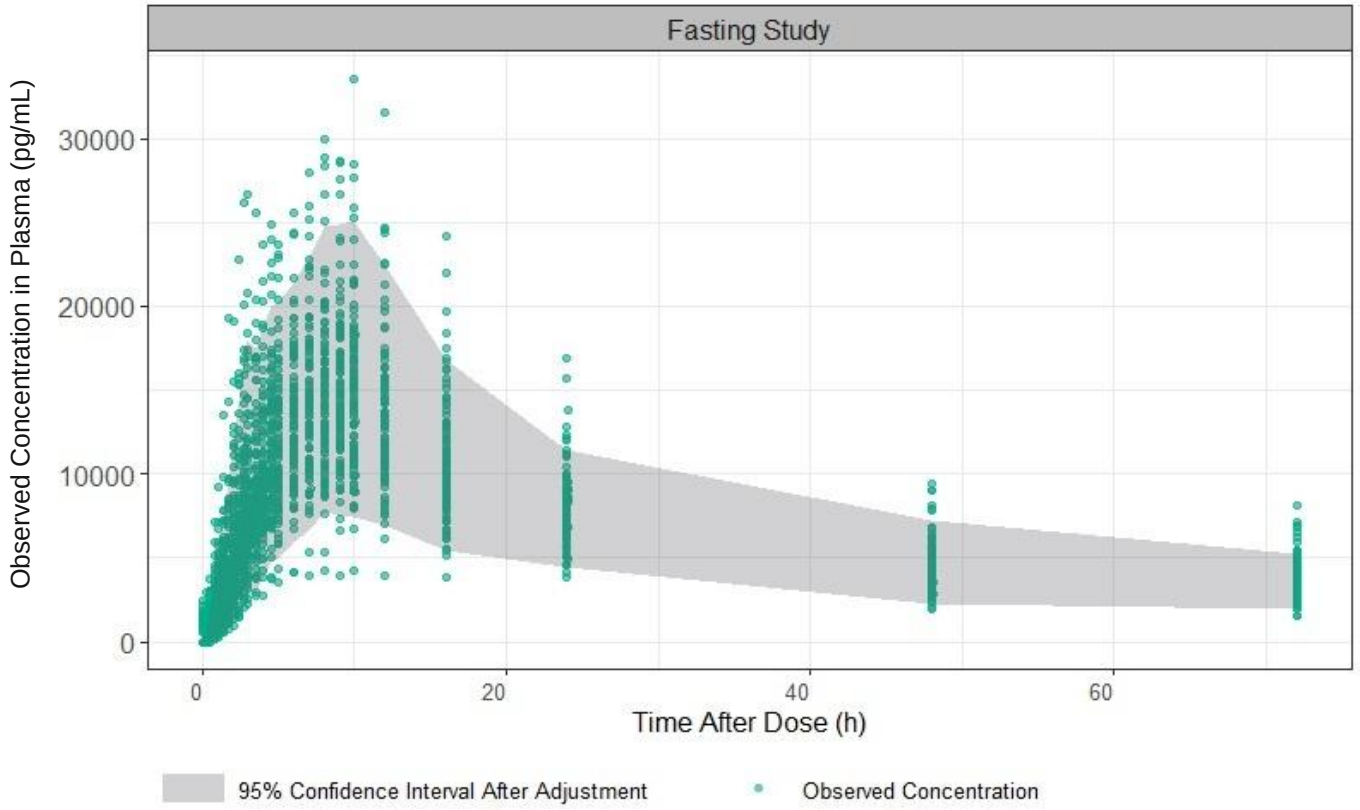
Example PK Profile for Demonstration Purposes



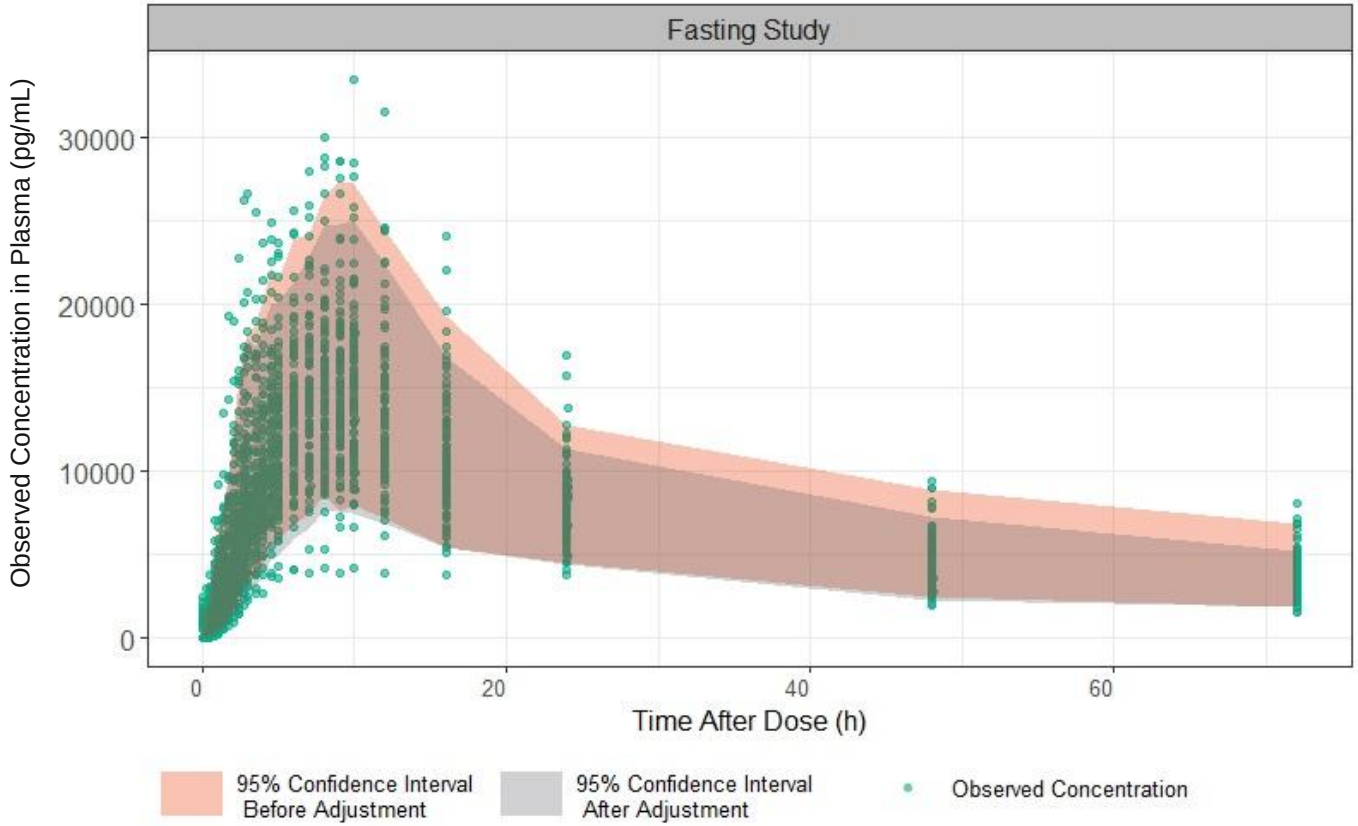
Pop PK Model-Based Concentration Adjustment Exemplary Result



Pop PK Model-Based Concentration Adjustment Exemplary Result

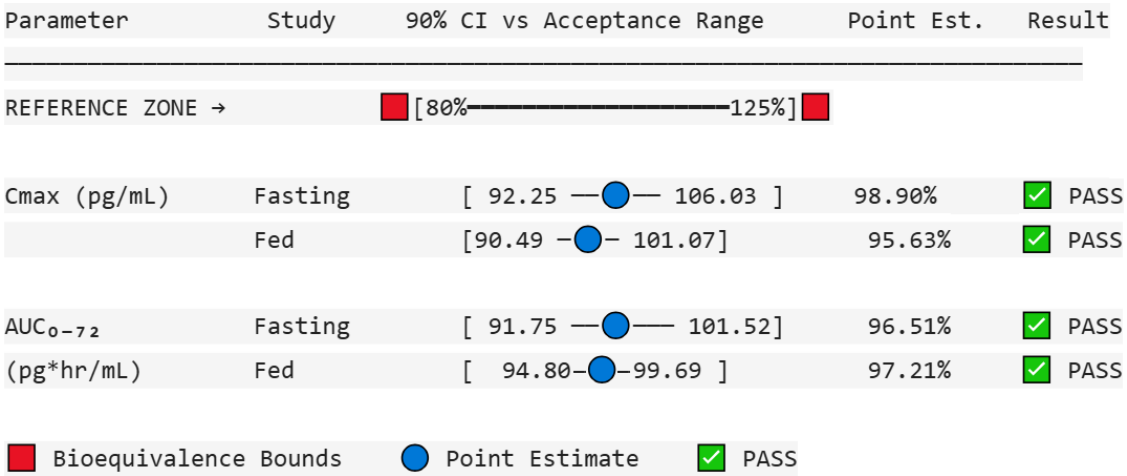


Pop PK Model-Based Concentration Adjustment Exemplary Result



MIE-Based Success: Bioequivalence Results

- Successful BE demonstration using MIE-based carryover adjustment
- All parameters met regulatory acceptance criteria after IPRED-based concentration corrections.
- Preserved complete dataset integrity by utilizing all available data



Implementation Recommendations: What FDA Expects

- Robust Model Building Process
  - Pop PK model developed using actual clinical data
  - Appropriate structural model selection and covariate inclusion
  - Adequate characterization of between-subject and residual variability
- Comprehensive Model Validation
  - Goodness-of-fit evaluations demonstrating model adequacy
  - Visual predictive checks confirming appropriate model performance
  - Individual-level predictions showing reasonable accuracy for carryover estimation
  - Validation that modeling approach produces results comparable to conventional methods when carryover is not present
  - Sensitivity analysis
  - Demonstrated ability to detect differences between formulations

Summary: Enabling Future Success

Challenge and Solution

- Pop PK modeling provides a scientifically robust alternative that preserves data integrity and saves BE studies that might otherwise fail.
- Pop PK modeling can successfully correct PK profile for time-varying residual concentrations of a long half-life drug with incomplete washout, resulting in adequate BE studies.
- Similar methodologies may be useful in other cases for drugs with long elimination half-life.
- Real-world success stories demonstrate that MIE-based approaches are proven pathways to successful ANDA approval.

Proactive Engagement with FDA is Key to Success

- Engage with FDA early through the MIE Pilot Program
  - (MIE@fda.hhs.gov)

MIE Pilot Program

Launched on October 1st, 2023

Dedicated regulatory platform for interactions on MIE

- Early and focused interactions between industry and FDA
- MIE-based approach for BE establishment in generic development

- Enhances scientific communications
  - Quantitative methods and modeling techniques
  - Address generic drug development issues
  - Questions cannot be sufficiently addressed by pre-ANDA and ANDA meetings. E.g.,
    - Common modeling issues across multiple products
    - Complex modeling approaches for non-complex products

MIE Pilot Program General Principles Document

Prepare An Effective MIE Meeting Request Package

- Sufficiently developed scientific proposal
  - Meeting questions are relevant, critical, and clearly stated
- Adequate documentation of the modeling approach
  - Purpose of the MIE approaches and how it will be used to address the question of interest and inform regulatory decision-making
  - Sufficient details for underlying assumptions and model building process
  - Clear model verification and validation strategies including current and future data support
  - Risk analysis/assessment
  - Model files and supporting datasets

See details in SBIA Presentation by Eleftheria Tsakalozou, Ph.D., Considerations and Expectations when Meeting with the FDA under the Industry Meeting Pilot MIE program, 1/18/2024

Resources

- ICH M13A Bioequivalence for Immediate-release Solid Oral Dosage Forms (Oct 2024)
- Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drug Submitted under an ANDA (Aug 2021)
- Guidance for Industry: Population Pharmacokinetics (Feb 2022)
- General Principles Pilot Program: Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants
- SBIA Workshop: A Deep Dive: FDA's Model-Integrated Evidence (MIE) Industry Meeting Pilot Program for Generic Drugs, January 18, 2024

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Questions?

Min Tzu Chung, PharmD
Pharmacokineticist
DBIII
OB, OGD
CDER | US FDA

Deniz Ozdin, Ph.D., M.Sc., BPharm
Pharmacologist
DQMM
ORS, OGD
CDER | US FDA

Updates and Current Landscape for Study Population Selection and Additional Mitigation Strategies in Bioequivalence Studies

Karen Li, PharmD and Duyen Nguyen, PharmD
Clinical Safety and Human Subject Research Team
Division of Therapeutic Performance II/Office of Research and Standards
Office of Generic Drugs/Center for Drug Evaluation and Research

Advancing Generic Drug Development Workshop: Translating Science to Approval
October 7-8, 2025

Disclaimer

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Purpose

To provide updates on specific considerations pertaining to subject safety in pharmacokinetic (PK) bioequivalence (BE) studies, specifically on:

- Re-assessment of patient-based product-specific guidances (PSGs)
- Additional features to ensure subject safety in healthy subject-based studies:
  - Pharmacogenetics (PGx) considerations, and
  - Use of concomitant medications (i.e., antiemetics)

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Re-assessment of Patient-Based PSGs

Background

Guidance for Industry: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Oct 2024)

"…To reduce variability not related to differences between drug products, the studies should normally be performed in healthy subjects unless the drug carries safety concerns that make this approach unethical... If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy subjects, the study may instead be conducted in a targeted patient population under suitable precautions and supervision."

"If the highest strength of a drug product cannot be administered to healthy subjects for safety and/or tolerability reasons, a single-dose study in healthy subjects using a lower strength may be acceptable."

Clinical Assessment Factors for Study Population Selection in PSG Development

- Nonclinical toxicology profile
- Safety data in patients and healthy subjects (if available) from NDA, ANDA, post-marketing data, and public reports (e.g., literature)
- Drug exposure at the dose intended for BE studies
- Relevant safety profiles of other drugs within the same class
- Pharmacological plausibility

NDA - new drug application; ANDA - abbreviated new drug application

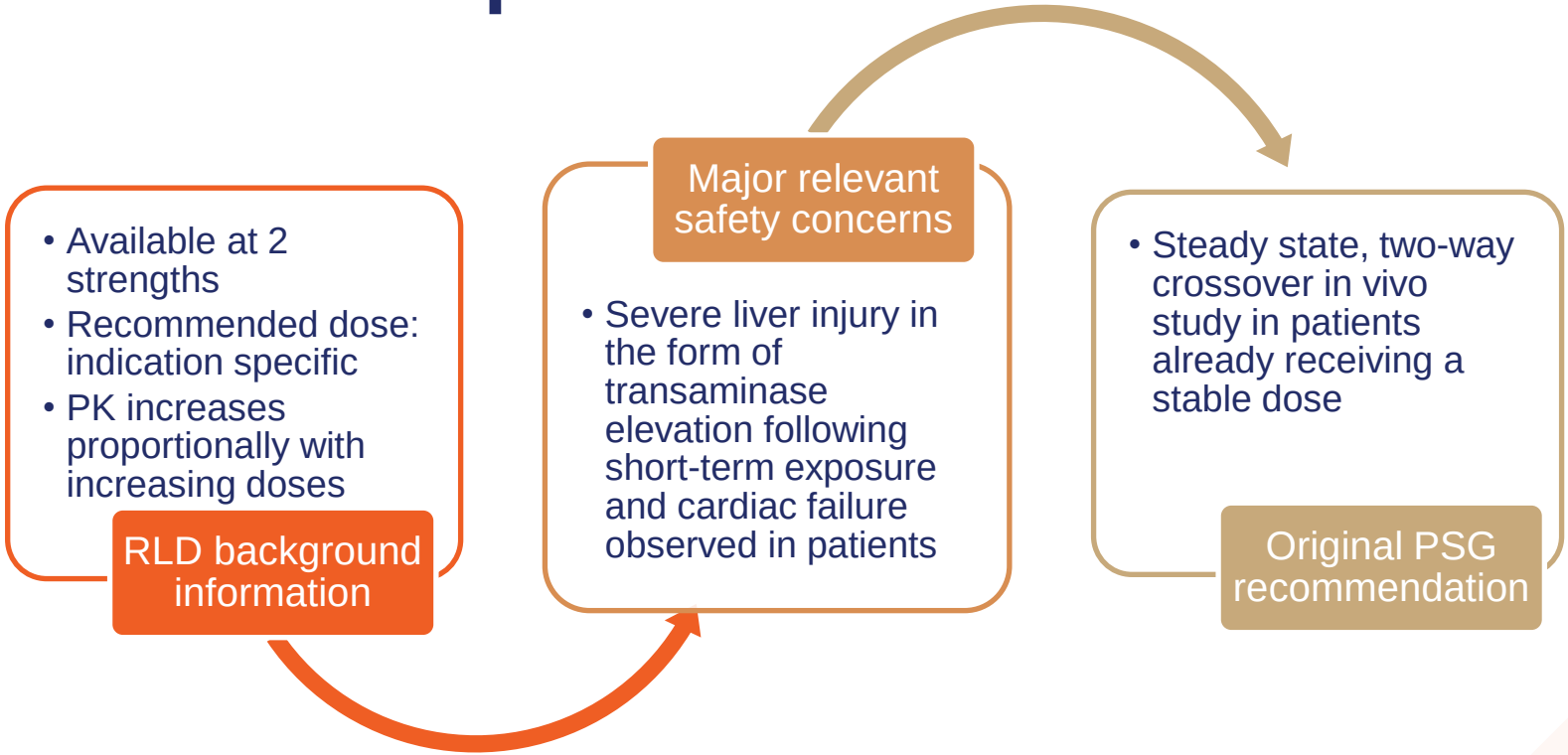
Core and Common Safety Criteria to Guide Study Population Selection for PK BE Studies

- Cytotoxicity (direct cellular damage)
- Genotoxicity and carcinogenicity (potential for primary malignancy)
- Reproductive toxicity (embryo-fetal toxicity and fertility impairment)
- Hepatotoxicity
- Cardiac related (arrythmias including QT prolongation)
- Hypersensitivity (severe skin reactions)
- Blood dyscrasia (immune function and bleeding risk)
- Effects on central nervous system (cognitive impairment)

Mitigation Strategies Adopted in PSGs to Enhance Subject Safety for Healthy Subject-Based Studies

Strategy	Examples
Reduce exposure to healthy subjects	Lower strength for BE studies, parallel study design
Exclusion criteria	Exclude subjects with abnormal liver function tests or with risk factors for prolonged QTc interval and Torsades de pointes
Targeted monitoring	Monitor liver function tests
Subpopulations	Males or females not of reproductive potential, exclude geriatric subjects
PGx factor (if appropriate)	Exclude certain subjects due to safety or PK reasons
Concomitant medications	Use of antiemetics

Re-assessment of Patient-Based PSGs: Example 1



Re-assessment of Patient-Based PSGs: Example 1 (cont.)

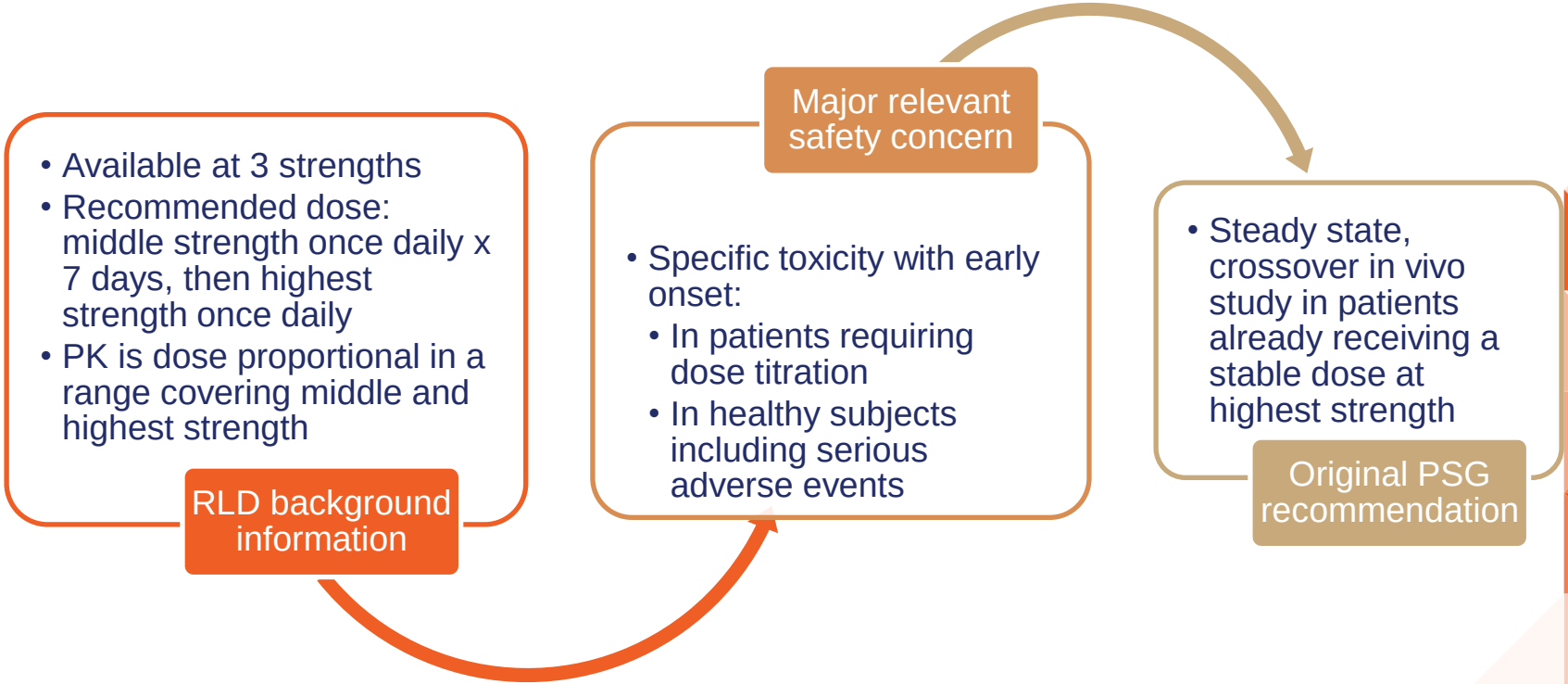
Cumulative data in healthy subjects from NDA and ANDA programs

- Additional safety data in healthy subjects received since the original PSG publication supported healthy subject enrollment
- Majority of adverse events (AEs) were mild to moderate in severity and generally manageable

Drug-exposure response relationship for safety risks

- The incidence and severity of hepatic and cardiac abnormalities in healthy subjects were higher at highest strength compared to the lower strength

Re-assessment of Patient-Based PSGs: Example 2



Re-assessment of Patient-Based PSGs: Example 2 (cont.)

Pre-approval data in patients

- Incidence was dose-related and occurred within 7 days of initiation

Pre-approval data in healthy subjects

- 4-fold higher number of AEs of potential toxicity in subjects receiving single doses of highest strength vs. middle strength of similar sample sizes
- All AEs of potential toxicity in subjects receiving single doses of middle strength were mild and manageable with non-pharmacological modalities

Post-approval data in patients

- No cases were reported in real-world setting (i.e., following approved titration regimen)

Additional Features to Ensure Subject Safety in BE Studies: PGx Considerations

"Phenotyping and/or genotyping of subjects may be considered for safety or PK reason." - *Guidance for Industry: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Oct 2024)*

Why PGx Considerations Matter in PK BE Studies

- Exclude subjects at higher risk for AEs related to genetic variations in drug metabolism
- Mitigate exposure-dependent or severe AEs
- Optimize crossover study design for drugs with long elimination half-life (e.g., adequate washout period, intersubject variability)
- Ensure balanced group allocation in parallel study designs

Current Implementation of PGx in PK BE Studies

- Over 390 drugs [counted per active pharmaceutical ingredient] contain PGx information in FDA labeling*
- 17 published PSGs include PGx recommendations
- Common enzymes involved:
  - CYP enzymes (n=9): CYP2D6, CYP2C19, CYP2C9
  - Non-CYP enzymes (n=8): G6PD, DPD, TPMT, NUDT15

CYP – cytochrome P450; G6PD – glucose-6-phosphate dehydrogenase; DPD – dihydropyrimidine dehydrogenase; TPMT – thiopurine methyltransferase; NUDT15 – nudix hydrolase 15

*Table of Pharmacogenomic Biomarkers in Drug Labeling. Available at https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Key Considerations for Integrating PGx into PSGs

- *Effect of polymorphic enzymes on drug PK (PK variability based on genotype)*
- *Effect of genetic variation on drug safety across genotypic subgroups*
- *Labeling contraindication or requirement for testing of polymorphic enzymes prior to the treatment initiation*
- *Clinical/PK implications of PGx in healthy subjects for PK BE studies (e.g., safety or study design related)*

Example: PGx-Based Subject Exclusion Due to Labeling Contraindications and Dosage Adjustments in Specific Genotypes

- Siponimod, a sphingosine 1-phosphate receptor modulator, is indicated for treatment of relapsing forms of multiple sclerosis
- Siponimod is available as 0.25 mg, 1 mg, and 2 mg tablets
- The labeling recommends
  - Test patients to determine CYP2C9 genotype before treatment initiation
  - Avoid use in patients with a CYP2C9*3/*3 genotype [contraindication]
  - Reduced maintenance dose in patients with a CYP2C9*1/*3 or *2/*3 genotype
- Siponimod AUC was approximately 61%, 91%, and 285% higher in CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 subjects
- Mean half-life is prolonged in CYP2C9*2/*3, and CYP2C9*3/*3 subjects

Example: PGx-Based Subject Exclusion Due to Labeling Contraindications and Dosage Adjustments in Specific Genotypes (cont.)

- **Current PSG recommendation**
  - *"Exclude subjects with CYP2C9*3 allele, such as CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3"*

Rationale for PGx comment	• 2- to 4-fold higher exposures in CYP2C9*3 allele carriers • Contraindicated in CYP2C9*3/*3 genotypes and recommends dosage adjustment for CYP2C9*1/*3 and *2/*3 genotypes • Minimize carryover effect following a crossover study • Ensure balanced groups of subjects in a parallel study

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Additional Features to Ensure Subject Safety in BE Studies: Concomitant Antiemetics

Why Concomitant Antiemetics Matter in BE Studies

- Gastrointestinal (GI) events such as nausea and vomiting are among the most commonly reported adverse reactions in BE studies conducted in healthy subjects and significantly affect their tolerability and compliance.
- Vomiting within a specific timeframe can impact absorption of oral drug products and increase the variability in PKs, potentially requiring removal of subjects from PK analysis to avoid confounding the BE conclusions.
- Mitigation strategies for vomiting in BE studies for high-emetogenic drugs may be crucial to subject retention and sample size estimation. Although concomitant medication is generally prohibited in BE studies in healthy subjects, concomitant antiemetics may be considered provided that its use does not compromise study integrity or affect BE outcomes.

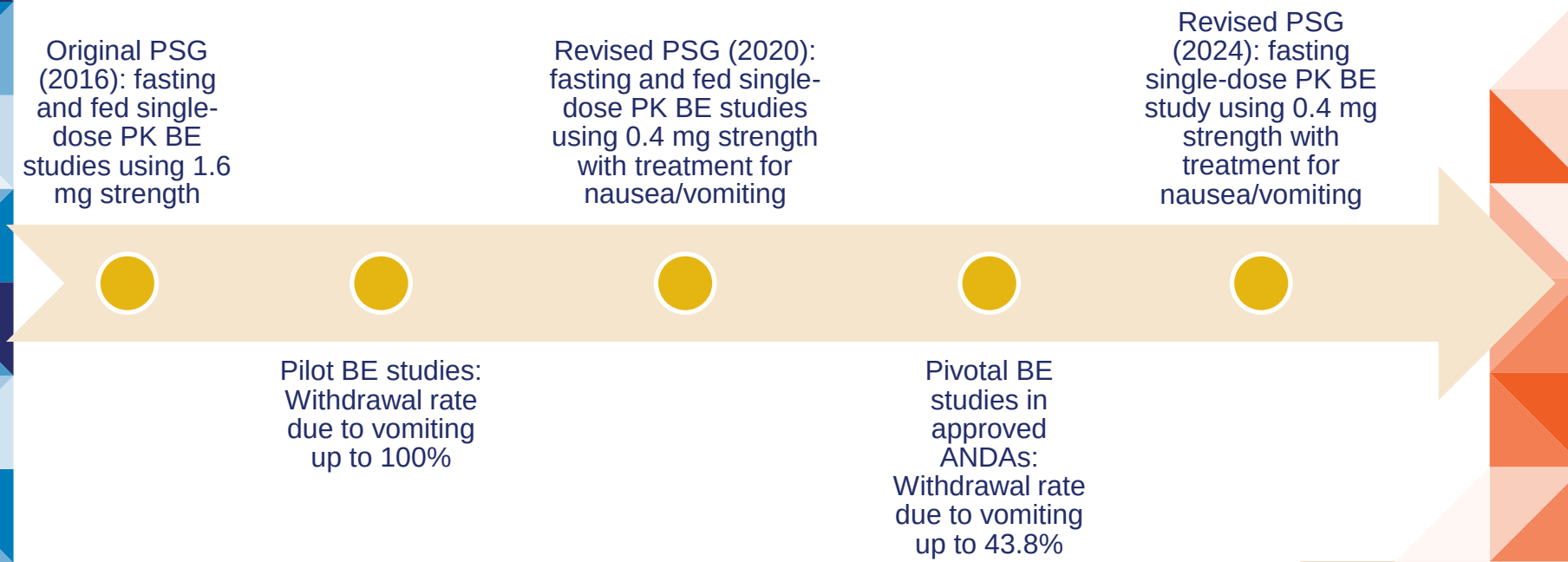
Current State and Considerations for Use of Antiemetics in PK BE Studies

- 5 published PSGs (3 active pharmaceutical ingredients) include antiemetic recommendations. Most corresponding BE studies incorporated antiemetics as recommended
- Considerations for use of antiemetics in BE studies:
  - Low risk of PK interactions with study drug (e.g., via absorption, elimination, GI motility)
  - Non-oral routes of administration (e.g., intramuscular, intravenous, transdermal)
  - Rationales for specific antiemetic and administration method should be provided in the protocol

Example: PSG Revision to Reduce Dose and Addition of Antiemetics

Drug Name, Dosage Form	Selexipag oral tablet
Strengths	0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, and 1.6 mg
Indication	A prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
Dosage and Administration	• The recommended starting dosage of UPTRAVI tablets is 0.2 mg given twice daily. • Increase the dose in increments of 0.2 mg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1.6 mg twice daily. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.

Example: PSG Revision to Reduce Dose and Addition of Antiemetics (cont.)



Summary

- Clinical assessment for the selection of BE study population and dose is based on nonclinical toxicology data, safety data from NDAs/ANDAs/post-marketing data/literature, drug exposure profiles, and pharmacological plausibility.
- Patient-based PSGs undergo re-evaluation based on accumulated safety data and evolving regulatory experience with specific drug products.
- The development of new PSGs and revision of existing PSGs incorporate emerging safety mitigation strategies for healthy subjects, including PGx factors, use of non-highest strength, and concomitant antiemetic therapy.
- Strategic study designs incorporating appropriate safety measures may be implemented to ensure subject safety without compromising regulatory decision-making.

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FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Extrapolation of Pharmacokinetics Bioequivalence to an Alternative Comparator Due to RLD/RS Unavailability

Advancing Generic Drug Development:
Translating Science to Approval 2025 Virtual Workshop

Yuqing Gong, Ph.D.

Senior Pharmacologist, Division of Quantitative Methods & Modeling (DQMM)
Office of Research and Standards (ORS), Office of Generic Drugs (OGD)
CDER | U.S. FDA

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Learning Objectives

- Discuss an alternative approach for establishing pharmacokinetics (PK) bioequivalence (BE) when the reference listed drug (RLD) or reference standard (RS) is unavailable.
- Analyze case studies that demonstrate the application of using an alternative comparator in BE studies.
- Learn how to calculate BE with this alternative approach through a step-by-step calculation demonstration.

BE Studies With PK Endpoints

To receive approval for an ANDA, an applicant generally must demonstrate among other things, that its proposed drug product is bioequivalent to the reference listed drug (RLD).[3] The FD&C Act provides that a generic drug is bioequivalent to the listed drug if:

> The rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.[4]

For most products, the focus of BE studies is on the release of the drug substance from the drug product into the systemic circulation. During such BE studies, an applicant compares the systemic exposure profile of a test drug product to that of the RLD designated in FDA's *Approved Drug Products with Therapeutic Evaluations* (the Orange Book).[5, 6]

Guidance for Industry, Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (August 2021)

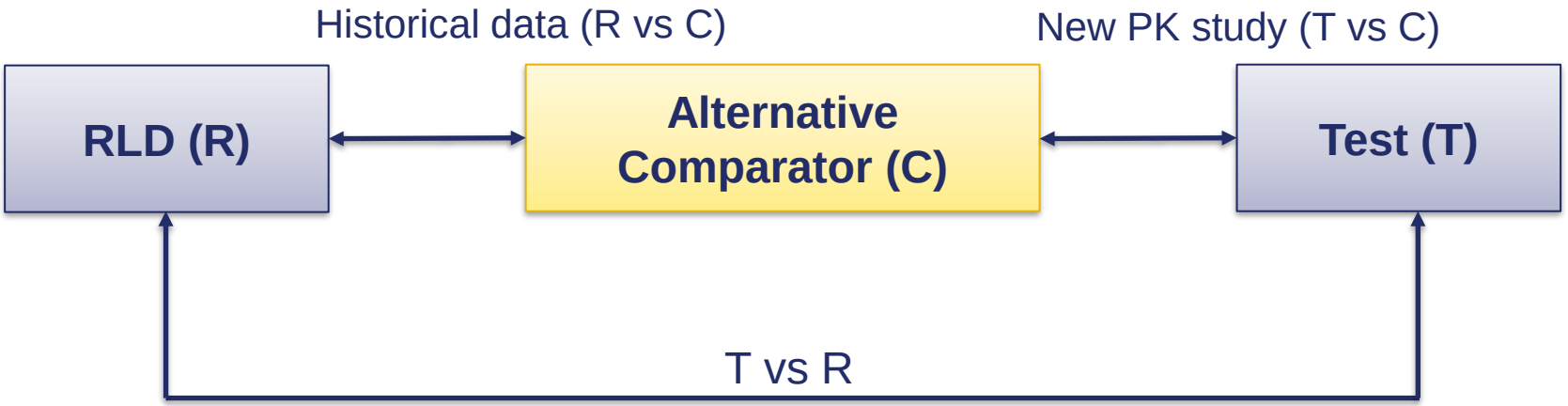
The reference standard (RS) selected by FDA is ordinarily the RLD. If FDA cannot select the RLD as the RS (e.g., RLD is withdrawn for reasons other than safety or efficacy), FDA may designate one of the generics as RS.

Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions (October 2020)

Alternative BE Approach – Extrapolating BE To An Alternative Comparator

- Conduct a relative bioavailability (BA) study with an alternative comparator and establish BE based on comparing the results with historical RLD data.
  - This alternative comparator can be a product with different dosage forms for the same route of administration.
  - Leveraging publicly available bridging studies conducted by the RLD holder during NDA submission.
- An alternative pathway to guide generic applicant interested in developing products when no RLD/RS is available in the market.

Extrapolating BE to An Alternative Comparator



The final BE decision should depend on whether the 90% confidence interval (CI) of the T/R ratio falls within 80.00%-125.00%.

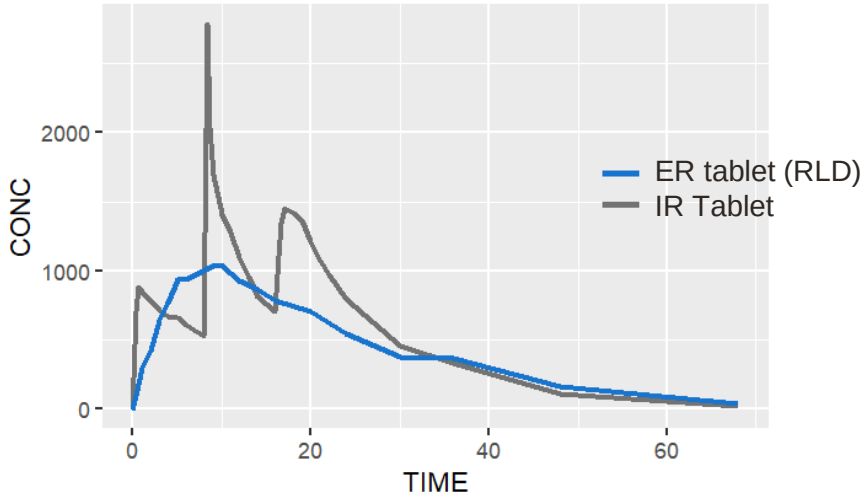
Case #1

- Drug product: oral suspension
- RLD/RS is not available
- The RLD was approved as a New Drug Application (NDA) through the 505(b)(2) pathway. The NDA holder demonstrated its oral suspension **is BE** to the oral tablet product (90% CI fall within 80-125%).
- **BE transitivity:** demonstrating BE between the test product (T) and the oral tablet formulation (serving as the alternative comparator, C) will establish BE transitivity across all three products (R, T, and C) in general.
- BE transitivity is a well-established approach commonly applied when a generic RS is used for in vivo BE comparisons in cases where the RLD has been discontinued from the market.

Case #2

- Drug product: extended release (ER) oral tablet
- RLD/RS is not available
- The RLD was approved as an NDA through the 505(b)(2) pathway. The NDA holder performed a relative BA study that compared its ER tablet to the immediate release (IR) tablet.
- **BE transitivity cannot be directly applied as R is not BE to the alternative comparator (i.e., IR tablet, C). However, the 90% CI of T/R can be extrapolated by leveraging historical and new study data to ultimately determine BE between T and R.**

Available Historical Data



- Two-way crossover PK study
- A single-dose ER tablet vs IR tablet, three times a day
- Following the same total daily dosage, BE between the ER tablet and the IR tablet (administered three times a day) was not demonstrated.

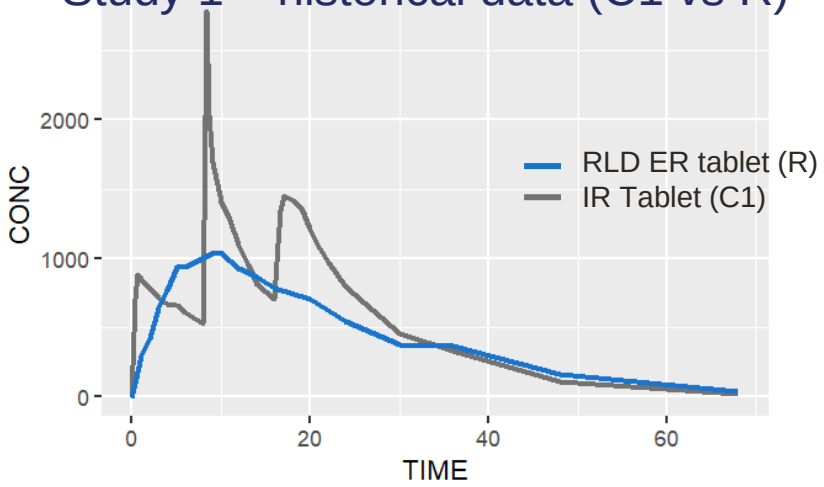
Summary of Statistical Analysis of PK Parameters (IR vs ER)

	GMR	90%CI	Sample size
Cmax	2.51	217.66-290.49	23
AUC(0-t)	1.24	113.25-134.83	23

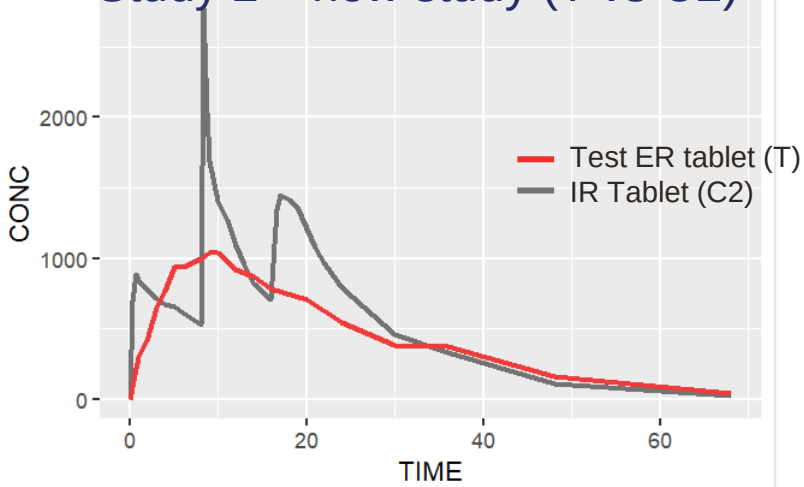
GMR- geometric mean ratio

Extrapolating BE Using IR Tablet As Alternative Comparator

Study 1 – historical data (C1 vs R)



Study 2 – new study (T vs C2)



- The alternative approach utilizes the relative difference, i.e., the geometric mean ratio (GMR) between two dosage forms (ER vs. IR).
- 90% CI for T vs R will be extrapolated based on their relative ratios compared to the IR tablet (i.e., T vs. C2 and C1 vs. R)

Statistical Analysis Method - Calculating Point Estimator

- Study 1 and 2 need to be conducted in a similar manner that satisfy the constancy assumption.
- An unbiased point estimator of the log-transformed geometric mean ratio of T/R (θ_{T_R}) can be calculated as

$$\hat{\theta}_{T\_R} = \hat{\theta}_{T\_C2} + \hat{\theta}_{C1\_R}, \qquad \textbf{Equation (1)}$$

where

$\hat{\theta}_{T\_C2}$ = estimate of log-transformed geometric mean ratio of **T** vs. **C2** from Study 2,
$\hat{\theta}_{C1\_R}$ = estimate of log-transformed geometric mean ratio of **C1** vs. **R** from Study 1.

See complete equations in Draft Guidance on Trazodone Hydrochloride (Recommended 10/01/2025)

Statistical Analysis Method - Calculating 90% CI

- Based on the testing results of equality of intra-subject variances between T and C2 and between C1 and R using an F test, calculate 90% CI of θ_{T_R} under either the homogeneous or heterogeneous assumption
- The following shows the equation of calculating 90% CI under the homogeneous variance assumption

$$\hat{\theta}_{T\_R} \pm t_{(0.95,\, df_{T\_R})} \times SE_p \,,$$

where $\hat{\theta}_{T\_R}$ is obtained from Equation **(1)**, and the standard error of $\hat{\theta}_{T\_R}$ and degrees of freedom under homogeneity (SE_p and df_{T_R}) can be calculated as

$$SE_p = \sqrt{MSE_p \times \frac{1}{2}\left(\frac{1}{n_{T\_C2,1}} + \frac{1}{n_{T\_C2,2}} + \frac{1}{n_{C1\_R,1}} + \frac{1}{n_{C1\_R,2}}\right)} \,,$$

$$df_{T\_R} = df_{T\_C2} + df_{C1\_R} \,,$$

SE = standard error
MSE = mean squared error
df = degrees of freedom
n1 =number of subjects in sequence 1
n2 =number of subjects in sequence 2

Statistical Analysis Method - Calculating 90% CI (cont.)

where

$$MSE_p = \frac{df_{T\_C2} \times MSE_{T\_C2} + df_{C1\_R} \times MSE_{C1\_R}}{df_{T\_C2} + df_{C1\_R}}$$

is the pooled mean squared error,

$n_{T\_C2,1}$ = number of subjects in sequence 1 from the study that compares **T** and **C2**,

$n_{T\_C2,2}$ = number of subjects in sequence 2 from the study that compares **T** and **C2**,

$n_{C1\_R,1}$ = number of subjects in sequence 1 from the study that compares **C1** and **R**,

$n_{C1\_R,2}$ = number of subjects in sequence 2 from the study that compares **C1** and **R**.

- 90% CI can also be calculated under the heterogeneous variance assumption depending on the results of the F test
  - 90% CI calculation under heterogeneous variance assumption are not shown in this presentation.

Example: Step-by-Step Calculation

	n (n1, n2)	GMR (θ, original scale)	90%CI (original scale)	θ (log-scale)	MSE
Study 1 C1/R (AUCt) Historical data	23 (11,12)	1.24	113.25-134.83	0.2116	0.0295
Study 2 T/C2 (AUCt) New study*	23 (11,12)	0.81	74.17-88.30	-0.2116	0.0295

*a hypothetical case example

n = total number of subjects
n1 = number of subject in sequence 1
n2 =number of subjects in sequence 2
MSE = mean squared error

Example: Step-by-Step Calculation

Calculate geometric mean ratio of **T/R** (θ_{T_R})

	n (n1, n2)	θ (log-scale)
Study 1 C1/R (AUCt) Historical data	23 (11,12)	0.2116
Study 2 T/C2 (AUCt) New study	23 (11,12)	-0.2116

→

	θ (log-scale)	θ (original scale)
T/R	0	1

$$\hat{\theta}_{T\_R} = \hat{\theta}_{T\_C2} + \hat{\theta}_{C1\_R}, \qquad \textit{Equation (1)}$$

Example: Step-by-Step Calculation

Test the equality of intra-subject variances between **T** and **C2** and between **C1** and **R** using an F test

	n (n1, n2)	MSE
Study 1 C1/R (AUCt) Historical data	23 (11,12)	0.0295
Study 2 T/C2 (AUCt) New study	23 (11,12)	0.0295

95% CI of $\sigma^2_{T\_C2}/\ \sigma^2_{T\_C2}$ is 0.4152-2.4086.

Because this 95% CI contains 1, we consider variances of two populations from study 1 and 2 are equal.

Calculate the 95% CI of $\sigma^2_{T\ C2}/\sigma^2_{C1\ R}$ as

$$\left[\frac{MSE_{T\_C2}/MSE_{C1\_R}}{F_{(0.975,\, df_{T\_C2},\, df_{C1\_R})}}, \frac{MSE_{T\_C2}/MSE_{C1\_R}}{F_{(0.025,\, df_{T\_C2},\, df_{C1\_R})}}\right].$$

Example: Step-by-Step Calculation

Calculate 90% CI of **T/R** (θ_{T_R})

	n (n1, n2)	θ (log-scale)	MSE
Study 1 C1/R (AUCt) Historical data	23 (11,12)	0.2116	0.0295
Study 2 T/C2 (AUCt) New study	23 (11,12)	-0.2116	0.0295
T/R	-	0	-

$$\hat{\theta}_{T\_R} \pm t_{(0.95,\, df_{T\_R})} \times SE_p \,,$$

where $\hat{\theta}_{T\_R}$ is obtained from Equation **(1)**, and the standard error of $\hat{\theta}_{T\_R}$ and degrees of freedom under homogeneity (SE_p and df_{T_R}) can be calculated as

$$SE_p = \sqrt{MSE_p \times \frac{1}{2}\left(\frac{1}{n_{T\_C2,1}} + \frac{1}{n_{T\_C2,2}} + \frac{1}{n_{C1\_R,1}} + \frac{1}{n_{C1\_R,2}}\right)} \,,$$

$$df_{T\ R} = df_{T\ C2} + df_{C1\ R} \,,$$

where MSE_p is the pooled mean squared error

$$MSE_p = \frac{df_{T\_C2} \times MSE_{T\_C2} + df_{C1\_R} \times MSE_{C1\_R}}{df_{T\_C2} + df_{C1\_R}}$$

90% CI of **T/R** is 88.64 – 112.81 (original scale)

BE between T and R is demonstrated

Summary

- We demonstrated an alternative approach for establishing BE through an alternative comparator (e.g., a product with a different dosage form for the same route of administration).
- The 90% CI for T/R will be extrapolated based on their relative PK ratios of both products compared to the alternative comparator. BE will be concluded if the extrapolated 90% CI for the T/R ratio falls within the acceptance criteria of 80.00%-125.00%.
- This approach provided an alternative method to guide generic applicant interested in developing products when no RLD/RS is available in the market.
- We strongly encourage applicants to engage in early communication with the FDA during product development (e.g., Model-Integrated Evidence Industry Meeting Pilot) if considering this alternative approach for demonstrating BE.

Model-Integrated Evidence (MIE) Industry Meeting Pilot

Launched on October 1st, 2023

The pilot program allows enhanced scientific communications on a broad range of quantitative methods and modeling techniques to address generic drug development issues or questions that are either out of the scope of or cannot be sufficiently addressed by the existing pre-ANDA and ANDA scientific meetings. E.g.,

- Common modeling issues across multiple products
- Complex modeling approaches for non-complex products

A dedicated regulatory platform for interactions on MIE

- To foster early and focused interactions between industry and FDA on MIE approaches for establishing bioequivalence (BE) in generic drug development

MIE Industry Meeting Pilot Between FDA and Generic Drug Applicants

MIE Pilot Program General Principles document

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Questions?

Yuqing Gong, Ph.D.

Senior Pharmacologist, DQMM
ORS, OGD
CDER | U.S. FDA