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

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

Disclaimer

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

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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

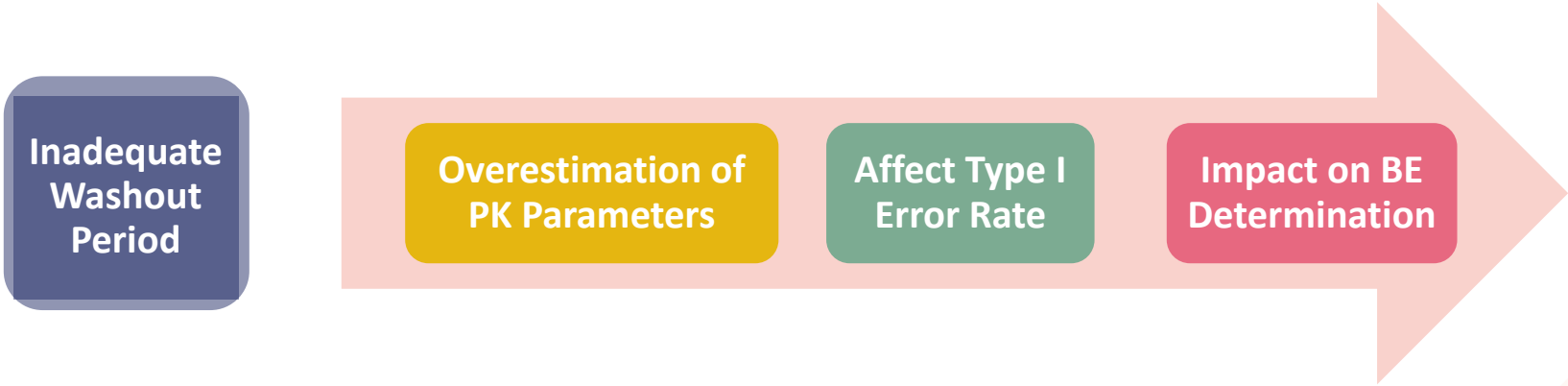
Elimination half-life ($t_{1/2}$)

≥ 24 hours

- 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

Drug Product	Oral IR Tablet - Contains two active pharmaceutical ingredients (APIs)
Applicant's *in vivo* Bioequivalence (BE) Study Design	• Single-dose, two-way crossover • Washout period (≥ 5 times of reported half-lives of two APIs) • 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 (for one of the API) • 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 becomes 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

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

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Pharmacologist, DQMM/ORS/OGD

The Solution – MIE Approach

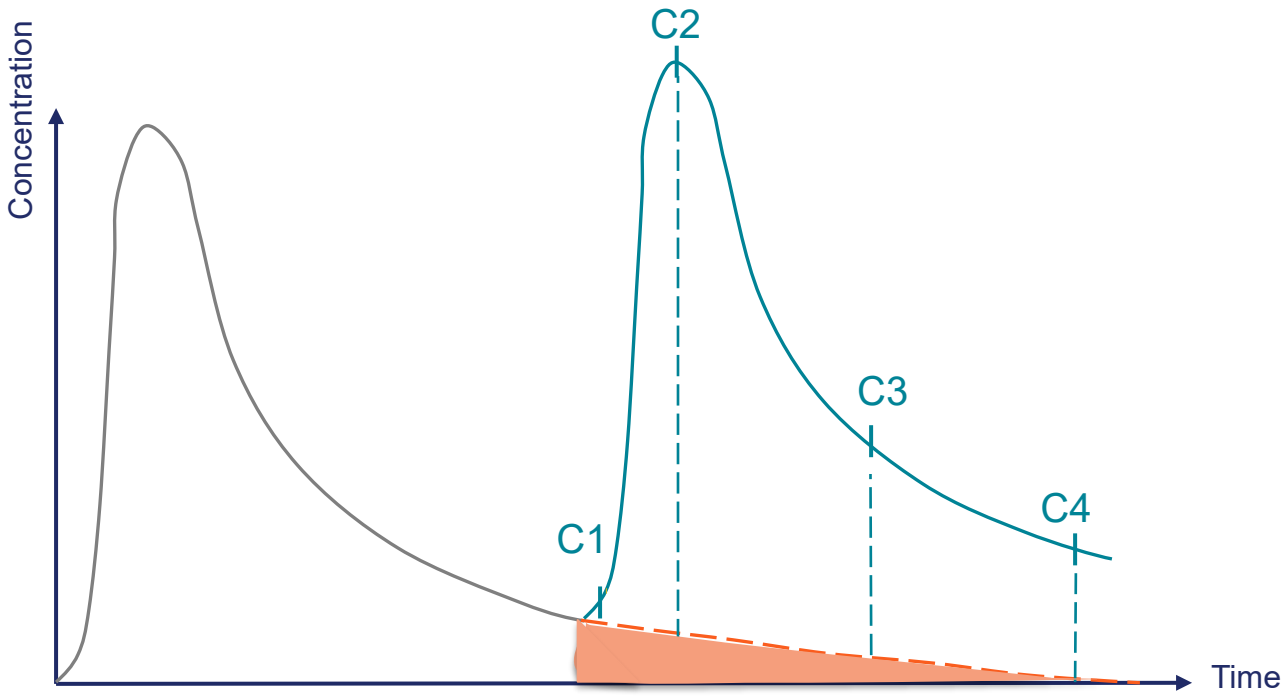
- Population PK (Pop PK) modeling provides a scientifically robust alternative to handle carryover
  - Individual-level predictions: Estimating residual drug concentrations from Period 1 for each subject
  - Precise adjustments: Removing predicted carryover effects from Period 2 observations
  - Preserved 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

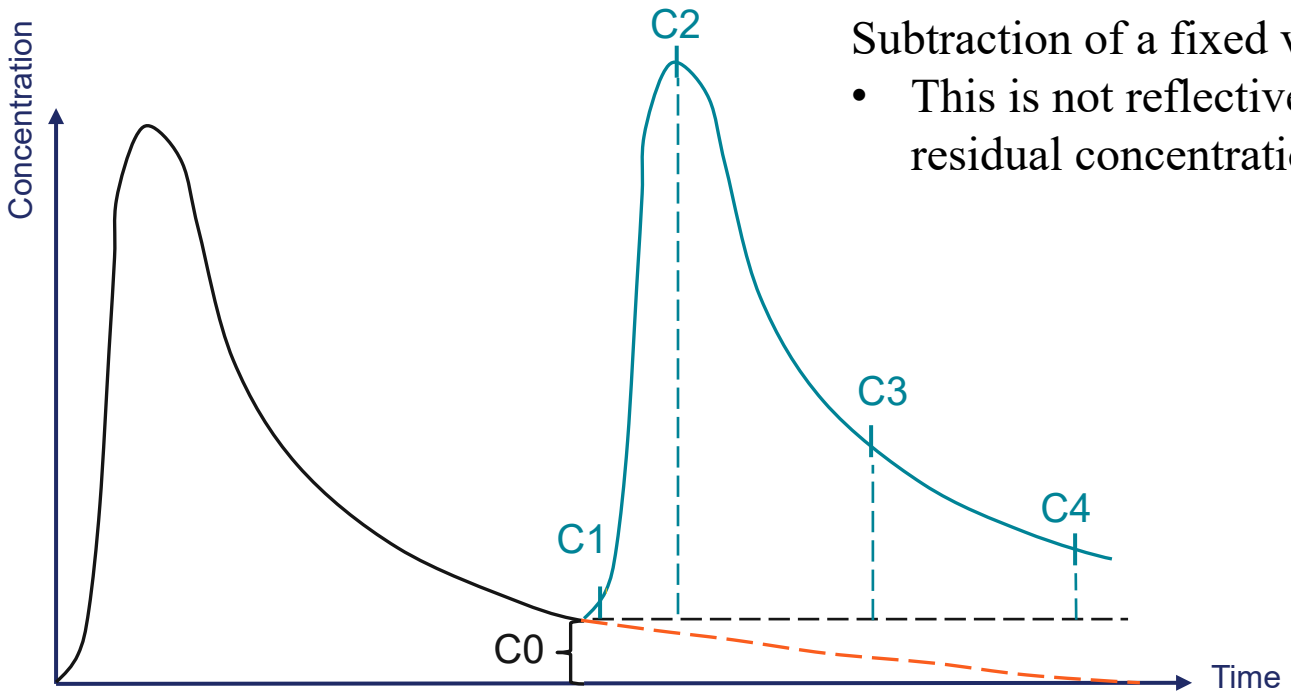
- Baseline Adjustment Approach:
  - Subtracts a fixed pre-dose value throughout Period 2
  - Limitation: Doesn't account for declining residual concentrations over time
- Pop PK model-based Concentration Adjustment:
  - Predicts time-varying residual concentrations
  - Advantage: Reflects actual PK decline 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.

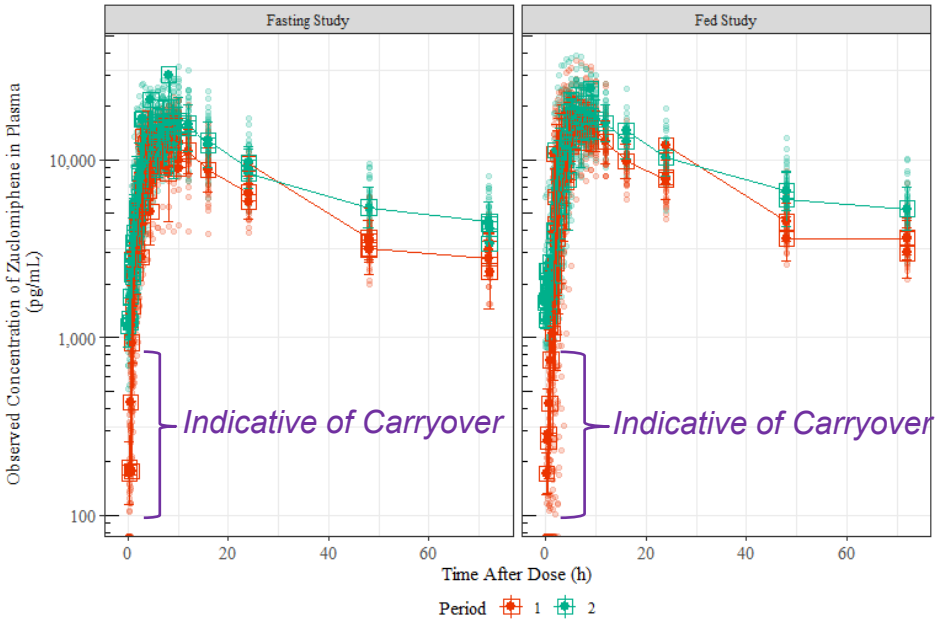
Baseline-Corrected Concentrations: C1-C0 C2-C0 C3-C0 C4-C0

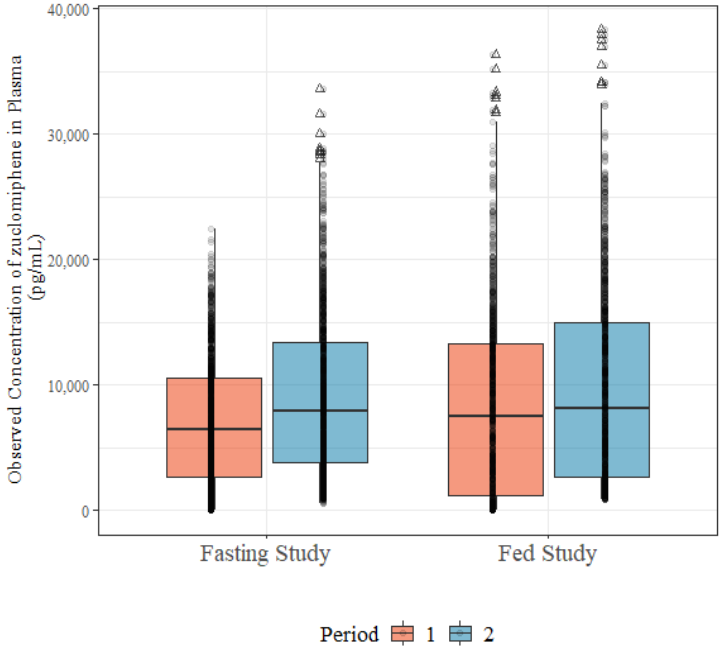
Real-World Success Story: Oral IR Tablet – Case 2 BE Studies

- **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
- Setting regulatory precedent for similar challenge

IPRED – Model-predicted individual predictions

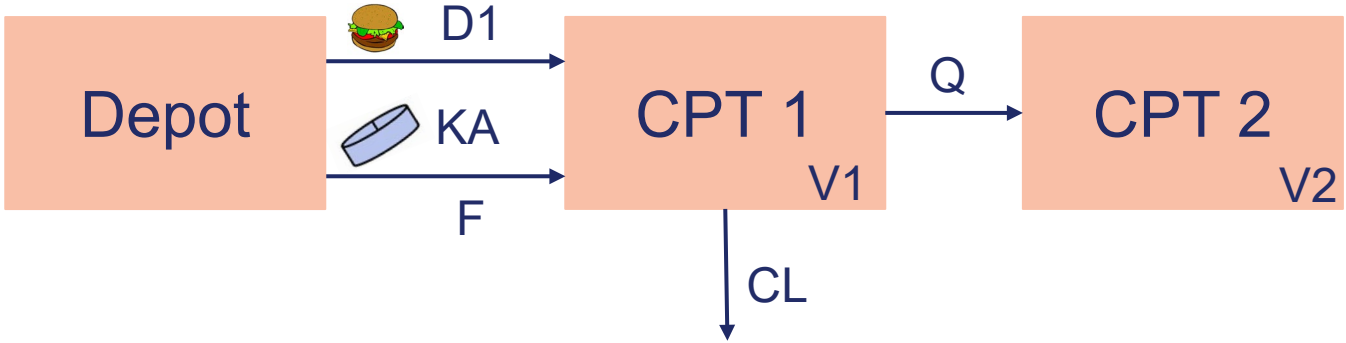
Pop PK Modeling - Data Exploration





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

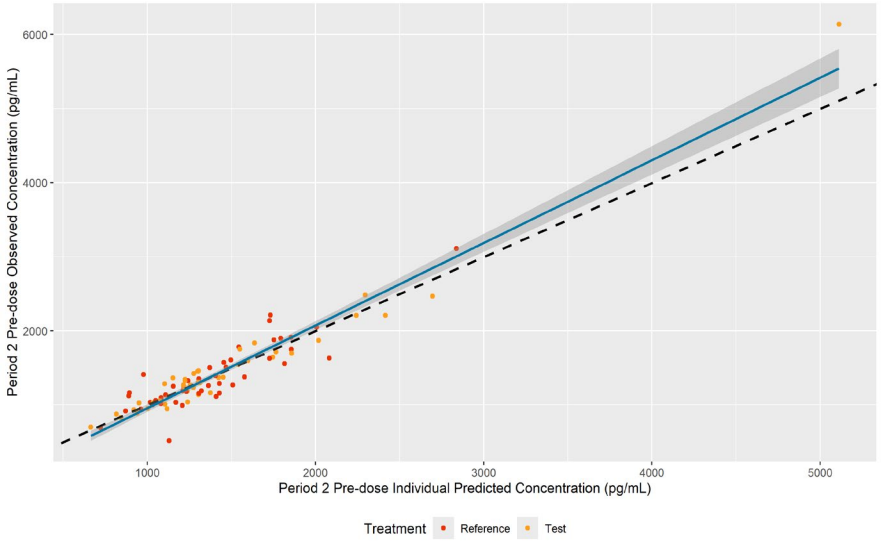


F: Apparent bioavailability (F/CL)
D1: Duration for depot CPT
CL: Clearance
Q: Intercompartmental clearance
V: Volume of Distribution
CPT: Compartment

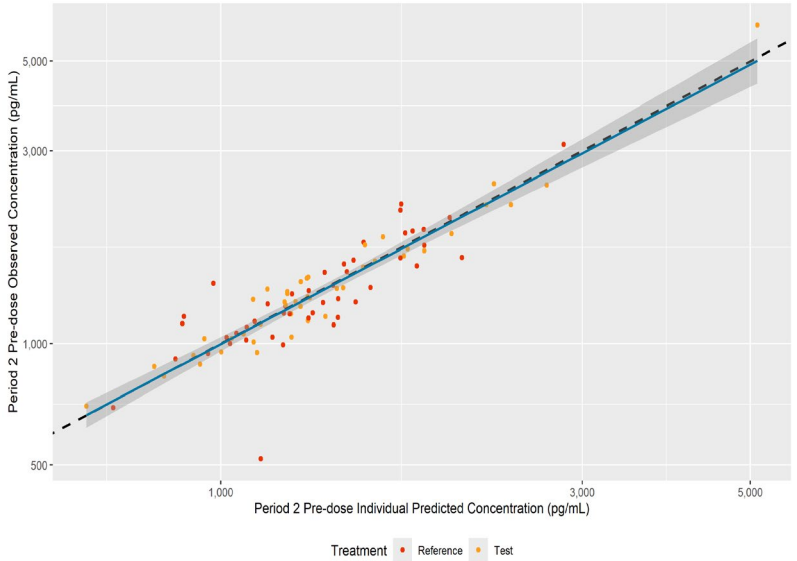
Pop PK Modeling – Model Diagnostics

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

Normal scale



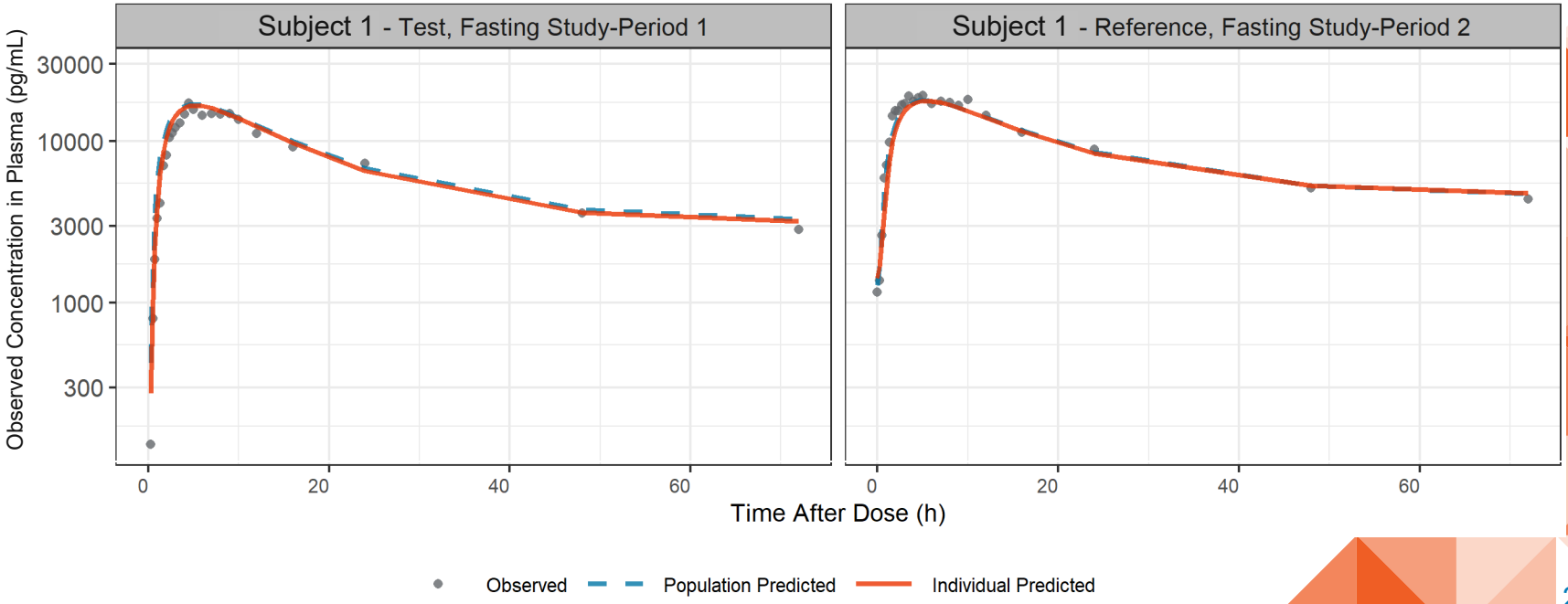
Log scale



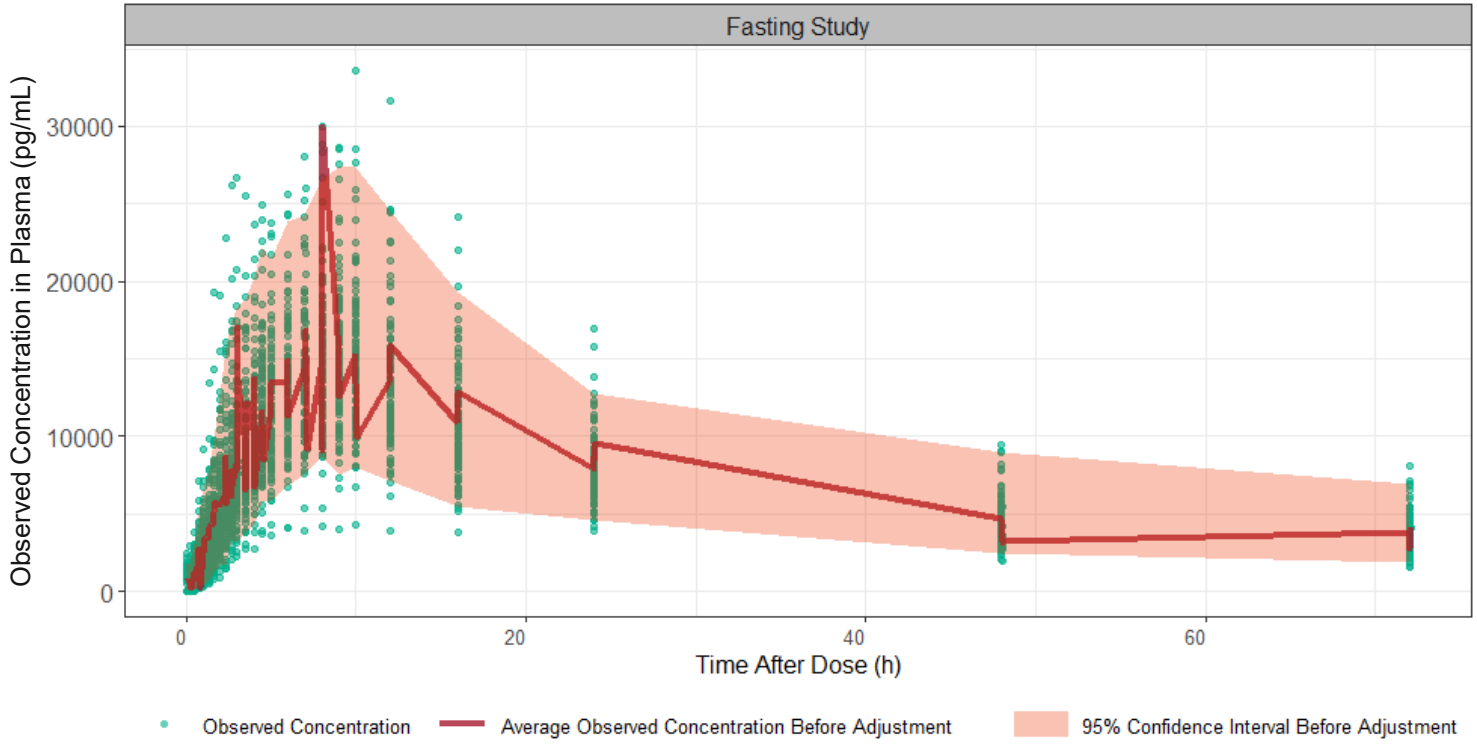
Pop PK Modeling – Model Diagnostics

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

Example PK Profile for Demonstration Purposes



Pop PK Model-Based Concentration Adjustment Exemplary Result



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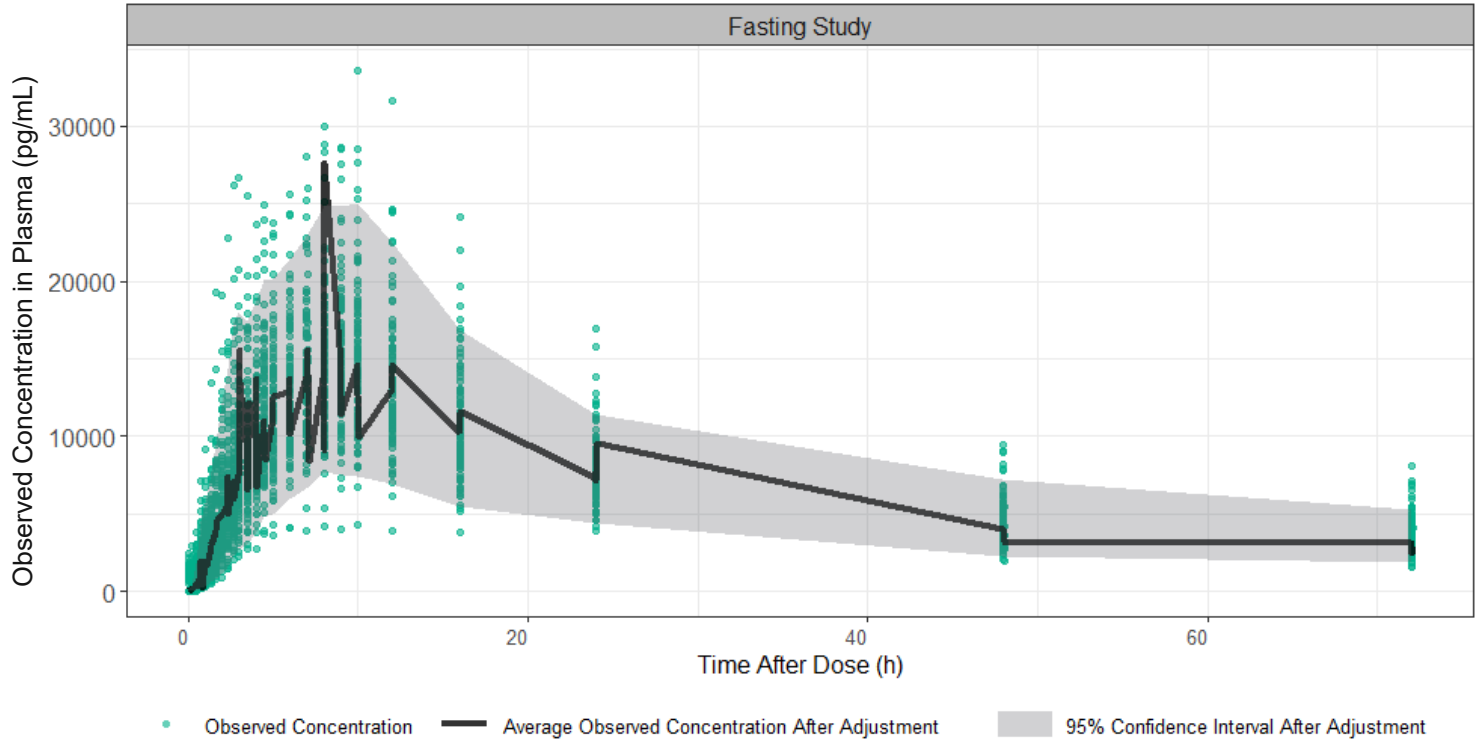
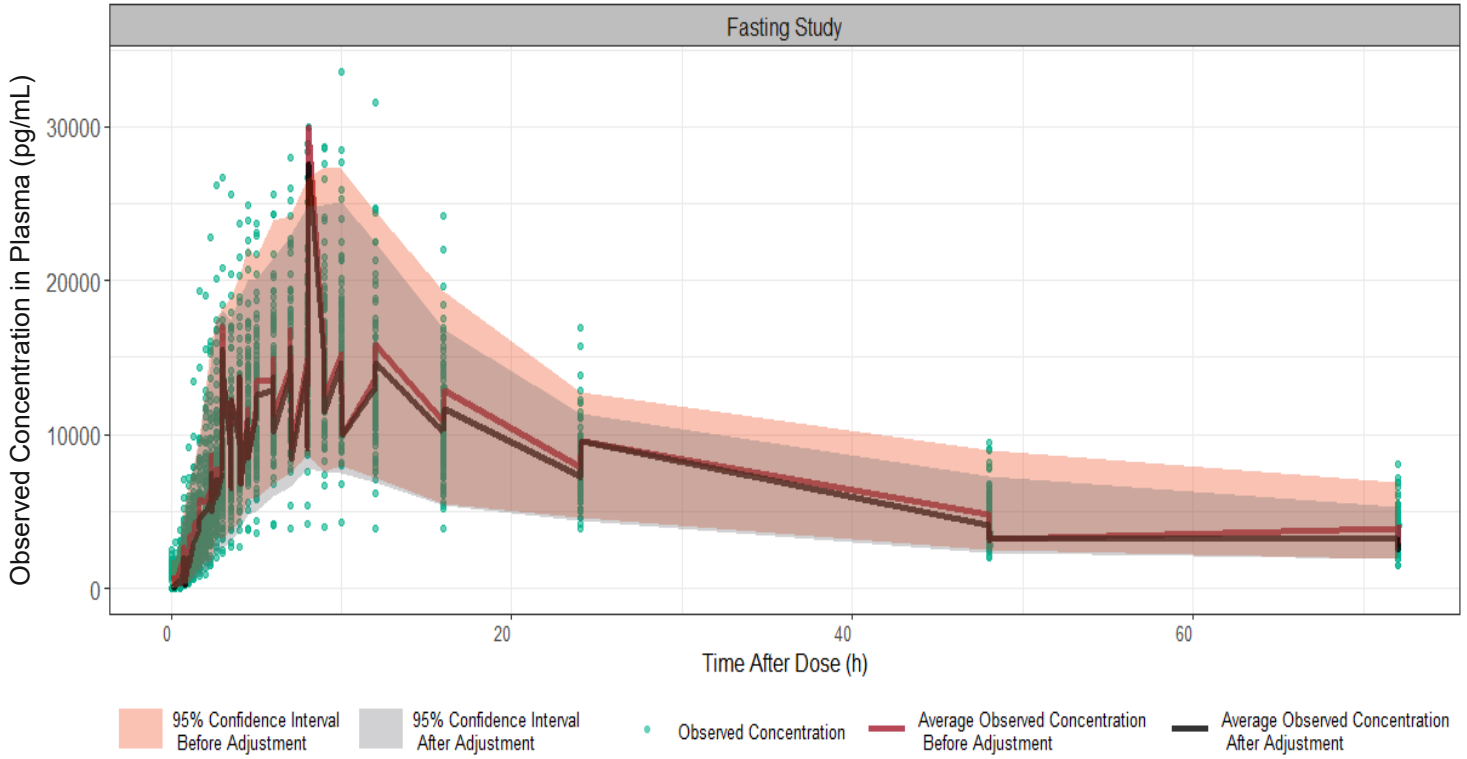


Pop PK Model-Based Concentration Adjustment Exemplary Result



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

Parameter	Study	90% CI vs Acceptance Range	Point Est.	Result
REFERENCE ZONE →		[80%——————125%]		
Cmax (pg/mL)	Fasting	[92.25 —●— 106.03]	98.90%	✅ PASS
	Fed	[90.49 –●– 101.07]	95.63%	✅ PASS
AUC_{0-72}	Fasting	[91.75 —●—— 101.52]	96.51%	✅ PASS
(pg*hr/mL)	Fed	[94.80–●–99.69]	97.21%	✅ PASS

■ Bioequivalence Bounds ● Point Estimate ✅ PASS

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 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
- 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

Questions?

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