Quantitative Clinical Pharmacology Tools to Support Generic Drug Development: Regulatory Expectations and Case Examples

Advancing Generic Drug Development (AGDD): Leveraging Model-Integrated Evidence (MIE) in the Development & Approval of Generic Drugs – August 27, 2026

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Outline

- Quantitative clinical pharmacology (QCP) tools in generic drug development
- Population pharmacokinetic (PopPK) modeling approaches to support pre-ANDA submissions and ANDA approvals
- Dose-scale analysis to support ANDA approval

QCP Applications in Generic Drug Development

Category	BE Study Topic/Challenge	QCP Tools/Approaches
Alternative PK study designs	• Large number of subjects (e.g., parallel design, HVD with long half-life) • Recruitment challenges of patient populations (e.g., orphan drugs, ophthalmic drugs, sensitive patient populations)	• Adaptive design • MIE/VBE
	• Long study duration (e.g., LAIs, long half-life drugs, steady-state design)	• Repeated crossover design (RRTT/TTRR) • Crossover with incomplete washout • Switch PK study • MIE/VBE
	• Sparse PK sampling (e.g., LAIs, ophthalmic drugs, special populations)	• MIE/VBE
	• Reference standard is discontinued	• PK BE bridging using alternative reference standard
	• Low post-dose concentration relative to endogenous baseline levels	• Alternative dose, study population, or pre-treatment
Study design and BE guidance clarifications	• Dose scale analysis for PD BE study	• Emax model development, validation, assessment
	• Comparative clinical endpoint BE study	• Dose and endpoint selection, sample size estimation
	• PK sampling scheme and washout period	• Optimal design, guidance, model-based methods
	• Endogenous baseline correction method	• Baseline patterns, sensitivity for BE, guidance/practice
	• BE approach for NTI drugs	• NTI drug assessment including PK/PD analysis
	• Missing samples and data imputation	• Model-based methods, sensitivity analysis, optimal design
	• Assessment of steady-state attainment in PK studies	• Statistical analysis, model-based methods
	• Dose scale analysis	• Emax model development and validation
Alternative BE metrics	• Alternative partial AUC metrics	• PK/PD analysis
	• Switch PK study	• Alternative BE limits based on MIE
	• Drugs with long half-life	• Suitability of AUC truncation
Statistical analysis and BE assessment	• Justification in deviations in PK profiles (e.g. Tmax, Tlag, multiple peaks)	• PK/PD analysis
	• Impact of covariates (e.g., parallel design)	• Covariate analysis in BE studies
	• Unbalanced data after data exclusion	• Data imputation, statistical analysis, sensitivity analysis
	• Patient BE study with different doses	• BE statistical analysis
	• Outlier data (e.g., 'statistical outliers')	• Data exclusion criteria, evaluation of model bias

BE: bioequivalence, PK: pharmacokinetic, PD, pharmacodynamic, MIE: model-integrated evidence, VBE: virtual bioequivalence, NTI: narrow therapeutic index, HVD: highly variable drug

Case Study #1: PopPK Model-Based Correction for Drug Carryover

Study Design

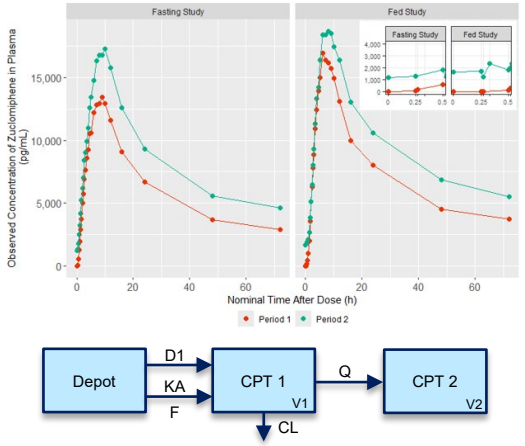
- PK BE study for clomiphene citrate oral tablet using a single-dose, two-way crossover design under fasting and fed conditions in healthy subjects
- Washout period of ~7 times the reported half-life of the RS

Issue

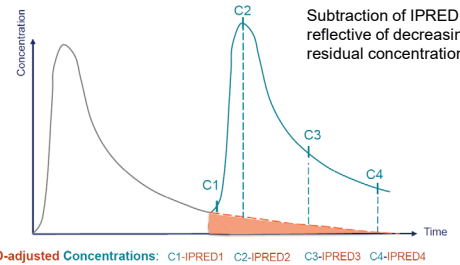
- In Period 2, most subjects had pre-dose concentrations > 5% of the respective Cmax values[1,2]
- **Insufficient data for statistical comparison** and BE demonstration after exclusion of data

QCP Approach

- FDA implemented **popPK model-based correction for carryover**
- Study met BE criteria using IPRED-adjusted concentrations



CPT: compartment, F: Apparent bioavailability (F/CL), KA, absorption rate constant, D1: duration for depot CPT, CL: clearance, Q: intercompartmental clearance, V: volume of distribution



www.fda.gov

RS: reference standard, IPRED: individual predicted

Adapted from presentation by Deniz Ozdin at SBIA Advancing Generic Drug Development Workshop: Translating Science to Approval Workshop on October 7, 2025

Case Study #2: PopPK Prediction of Terminal Elimination Phase (FDA)

Study Design

- PK BE study for NTI drug product using single-dose, four-way, fully-replicate crossover design in healthy subjects under fasting conditions

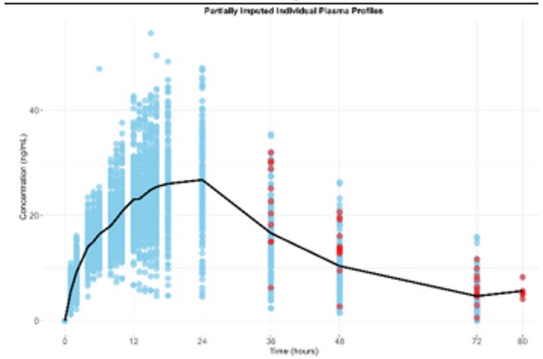
Issue

- Several subjects exhibited **inadequate characterization of the terminal elimination phase**[1,2]
- Study failed to meet BE criteria for AUCinf after excluding this data

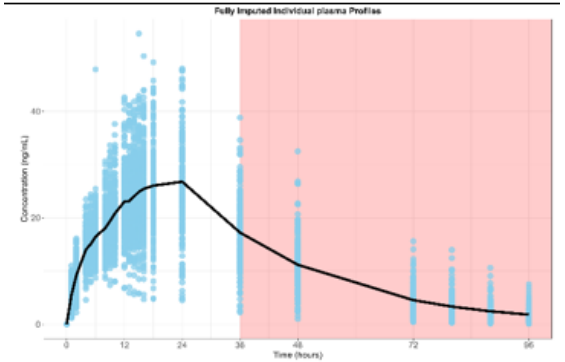
QCP Approach

- FDA implemented **popPK model-based prediction of PK profiles** in terminal elimination phase enabling more reliable estimation of Kel and AUCinf
- Enhances statistical power through BE assessment of more complete datasets

Partial Imputation



Full Imputation



Kel: apparent terminal elimination rate constant, AUCinf: area under the curve extrapolated to infinity

Adapted from poster presentation by Abdullah Shoyaib at Generic Drug Science Day 2026 on March 10, 2026

Case Study #3: PopPK Modeling to Address Missing Data from Study Interruption

Study Design

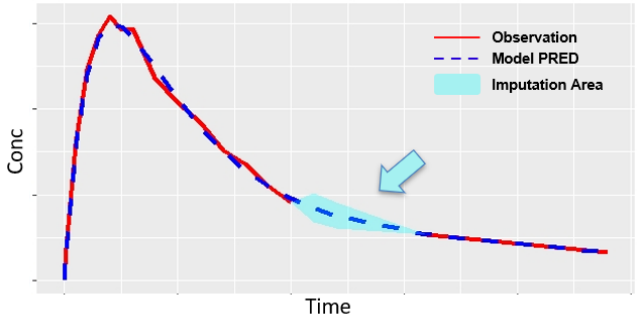
- PK BE study for LAI product using single-dose, parallel design

Issue

- PK data was not collected from a large number of subjects during part of the study due to study interruption

QCP Approach

- Applicant used **popPK modeling to impute missing data**
- BE assessment with imputed data was used for BE demonstration



Simulated time-concentration profiles for demonstration purpose

- **PopPK model was developed from the impacted study**
- **Data imputation is conducted at an individual level**
- **Missing points are filled by values estimated from the PopPK model with uncertainties estimated (presented as the imputation area)**

LAI: long-acting injectable

Adapted from presentation by Yuqing Gong at SBIA Advancing Generic Drug Development: Translating Science to Approval Workshop on September 21, 2022

Case Study #4: Repeated Crossover Design with Sparse Sampling or MIE BE

Recommended Study Design

- PSG for an oncology drug product recommends a PK BE study using a multiple dose, two-way crossover design in patients already receiving a stable dosing regimen

Issue

- Applicant described challenges with **recruitment in rare disease patient population** and **clinical concerns with multiple blood draws in patients** using replicate crossover designs

Proposed Study Design(s)

- Multiple-dose, **repeated crossover** design (TTRR/RRTT) with **sparse sampling**; or
- **MIE BE** approach using a popPK model developed from a **small number of patients**

QCP Approach

- Simulated VBE trials using popPK model and compared NCA/BE results under various optimized sampling schemes
- MIE BE approach was similar with methods developed under GDUFA research[3]

PSG: product-specific guidance, NCA: noncompartmental analysis, GDUFA: Generic Drug User Fee Amendments

Proposed MIE for BE Assessment from GDUFA Research Program[3]

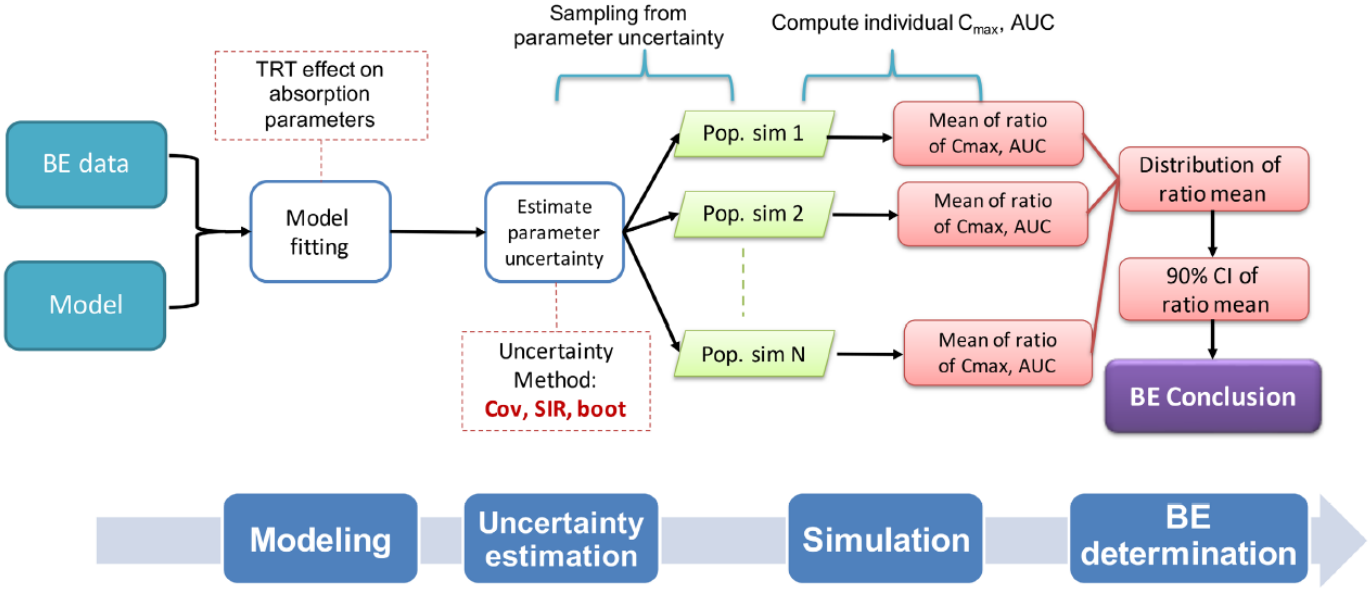


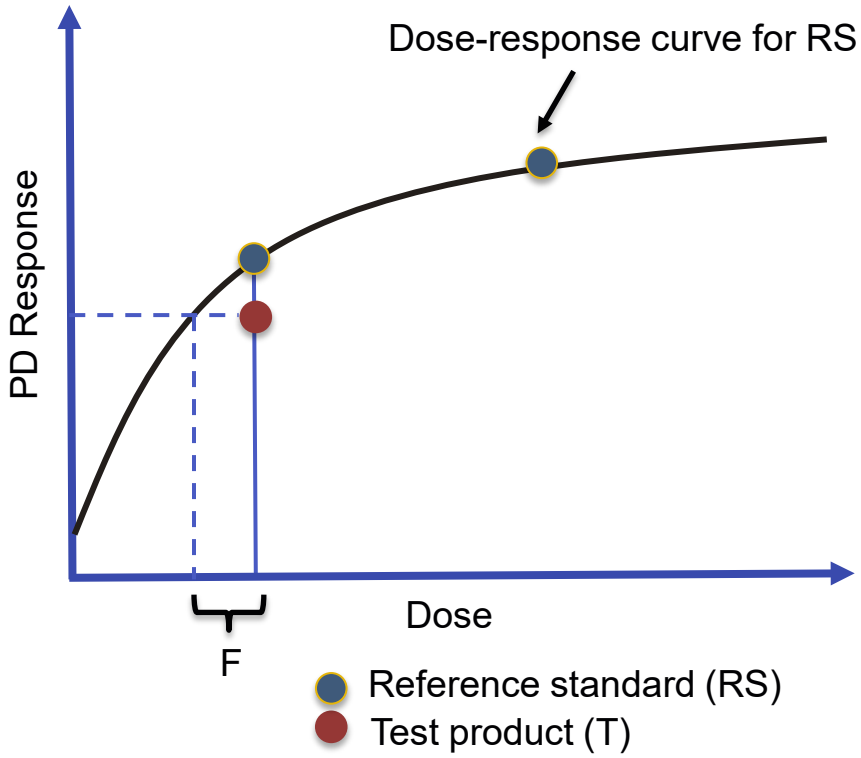
FIGURE 1 Overview of our developed model-integrated evidence approaches for bioequivalence (BE) analysis. The method consists of four steps: (1) model fitting using a pre-defined model for the reference product with additional treatment effect (TRT), sequence effect (SEQ), and period effect (PER) on absorption parameters including bioavailability (F, F is assumed to be 1 for the reference product); (2) uncertainty assessment using covariance matrix (Cov), sampling importance resampling (SIR), or nonparametric bootstrap (boot); (3) simulation for population (i.e., with a large subject number), which can be changed to simulation for a typical subject; and (4) conclusion based on the 90% confidence interval (CI) of the geometric mean ratio obtained from the simulation step.

Regulatory Expectations for PopPK Approaches Supporting BE

Category	Recommendations and Considerations
Study Design:	• Provide sufficient **justification for alternative BE approaches** that are not recommended in PSG • Provide sufficient justification for **sample size(s)** used in **model development** and **BE assessment**
Modeling Method/Software:	• PopPK using NLME modeling: fixed/random effects, sparse data, less sensitive to study design (Tmax) • Various modeling software: NONMEM, Monolix, Phoenix NLME, and others
Model Development/Validation:	• Pre-specify **modeling analysis plan** (MAP) • **Describe model development** (e.g., candidate models, criteria for model improvement, convergence) • Evaluate **model adequacy and performance** (e.g., GOF, VPCs, individual predictions, other criteria)[4] • Provided evidence that PopPK model is **sensitive to detect formulation differences** (e.g., Type I/II error)
Data Analysis/Assessment:	• Pre-specify **statistical analysis plan** (SAP) including method(s) for handling **missing data** and **BLQ data** • Pre-specify methods to address **inadequate sampling** or **inadequate characterization of PK profiles** • Evaluate imbalance of **missing/imputed data** across treatments, missing mechanisms, and impact on BE determination • Assess **sensitivity of BE determination** under different scenarios (e.g., single-dose vs. steady-state) • Evaluate impact of **parameter uncertainty** on BE assessment
Virtual BE Trials:	• Address concerns with potential **bias in model selection** (e.g., conventional model averaging, bootstrap model selection) • Provide sufficient **justification for sample size** used in virtual BE trials • Specify **BE metrics and acceptance criteria** for VBE trials [e.g., trials passing (%), distribution of GMRs]

GOF: goodness-of-fit, VPC: visual predictive check, GMR: geometric mean ratio

Dose–Scale Analysis for PD BE Study



- Nonlinear dose-response: PD response does not increase proportionally with dose

$$y = E_0 + \frac{E_{max} * Dose * F^i}{ED_{50} + Dose * F^i}$$

(Ref: $i = 0$; Test: $i = 1$)

Where y = Response, Dose = Administered dose, E_0 = Baseline response in the absence of the drug, E_{max} = Fitted maximum drug effect, ED_{50} = Dose required to produce 50% the fitted maximum effect, and i = Treatment indicator (0 = Ref, 1 = Test), with the understanding that $F^0 = 1$ and that F^1 is the relative potency used to evaluate bioequivalence.

- BE of drug products is assessed by estimating relative bioavailability (F) on dose scale, not original scale of PD response
- Suggests equivalence of the amount of drug reaching the site of action
- DSA is recommended in PSGs for demonstrating PD BE of:
  - Albuterol sulfate inhalation products
  - Levalbuterol tartrate inhalation aerosol
  - Orlistat oral capsule

Case Study #5: PD BE Study using DSA for Albuterol Sulfate MDI

BE Recommendations

- Option III: Two in vitro BE studies, one in vivo PK BE study with PK endpoints, and **one PD BE study**

PD BE Study Design

- Single-dose, double-blind, double dummy, randomized, crossover design in subjects with asthma

Concerns

- **Sample size was significantly lower** than planned due to study interruption
- **Variability** in PD data, **non-positive D-R** relationships, **AQL** data
- **Uncertainty** in PD parameter estimates

QCP Approach

- Evaluated adequacy of Emax model (e.g., model development, validation, context of use)
- Demonstrated model is sensitive to detect formulation differences (e.g., Type I/II error)
- Compared model parameter estimates and uncertainty, study power, and BE results to publicly available data
- Evaluated different imputation methods for AQL data
- Provided supportive VBE analysis
- Calculated 90% CI for Frel using two methods

MDI, metered dose inhaler, D-R: dose-response, AQL: above the quantitation limit, DSA, dose-scale analysis, CI: confidence interval

Regulatory Expectations for PD BE Studies Using DSA

Category	Recommendations and Considerations
Study Design:	• Consider **recommendations in PSG** for study design, population, inclusion/exclusion criteria, methods, and analysis • Provide sufficient **justification for alternative approaches** that are not in the PSG (e.g., VBE analysis) • Provide sufficient justification that **sample size is adequate** to develop reliable Emax model and perform DSA
Modeling Method/Software:	• **NLME modeling preferred**: fixed/random effects, less sensitive to aberrant observations, routinely used in applications • Various modeling software (NONMEM, SAS, R): Results generally consistent with same model structure/parameter settings
Model Development/Validation:	• **Describe model development** (e.g., candidate models, criteria for model improvement, convergence) • Evaluate **model adequacy and performance** (e.g., GOF, VPCs, individual predictions, other criteria)[4] • Evaluate **plausibility of PD parameter estimates** and compare results to published data if available • Provided evidence that Emax model is **sensitive to detect formulation differnces** (e.g., Type I/II error)
Data Handling:	• **Log transformation** of PD data should be specified and justified in the protocol • Avoid possibility of **negative values** (as appropriate) • Pre-specify method(s) for handling **dropouts, missing data, and AQL data**
Data Analysis/Assessment:	• Evaluate imbalance of **missing/imputed data** across treatments, missing mechanisms, and impact on BE determination • Investigate **non-positive D-R** relationships, imbalance between Test product and RS, and impact on model fit • Evaluate **impact of uncertainty** in PD parameter estimates on BE assessment
Computing 90% CI of F:	• Recommend following the **bootstrap procedure in the PSG** • Resample original dose-response observations at subject level (typical minimum of 1000 bootstraps) • Alternatively, **estimate 90% CI for F directly** from the point estimate of F and its SE calculated **using NLME modeling** • Prespecify modeling software and computation method for 90% CI

NMLE: non-linear mixed effects, DSA, dose-scale analysis, D-R: dose-response, AQL: above the quantitation limit, VBE: virtual BE, CI: confidence interval

Summary

- QCP approaches may be utilized to provide scientifically robust alternative BE approaches that preserve data integrity, enhance statistical power, and lead to approval of BE studies that might otherwise fail

- PopPK modeling approaches may be used to address challenges in PK BE studies with incomplete washout, inadequate sampling scheme, and missing data

- NLME modeling (Emax) may be used to address challenges with DSA to assess PD equivalence of albuterol sulfate MDIs

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* No longer in ORS/DQMM

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Questions?

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