Controlled Correspondence on Clinical Pharmacology Topics in Generic Drug Development

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CDER Small Business and Industry Assistance (SBIA) Webinar:
Navigating Controlled Correspondences to
Support Generic Drug Development

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Disclaimer

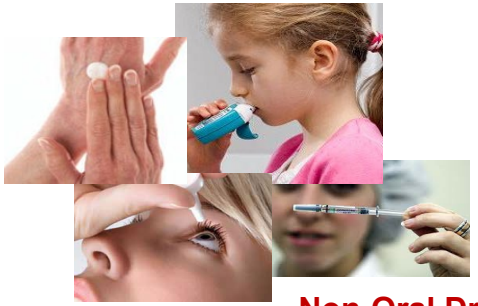
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Overview

- Controlled correspondence (CC) process
  - CC classification and timeline
  - Recommended practices for requestors
  - Focus on clinical pharmacology topics
- Case examples
  - Adaptive design for bioequivalence (BE) studies with pharmacokinetic (PK) endpoints or clinical endpoints
  - Alternative designs for BE studies with PK endpoints for long-acting injectable (LAI) products
- Alternative mechanisms for Agency feedback

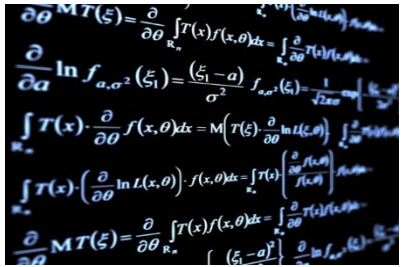
Quantitative Methods and Modeling in Office of Generic Drugs

PK – pharmacokinetics
PD – pharmacodynamics
PBPK – physiologically based PK
CFD – computational fluid dynamics
QCP – quantitative clinical pharmacology

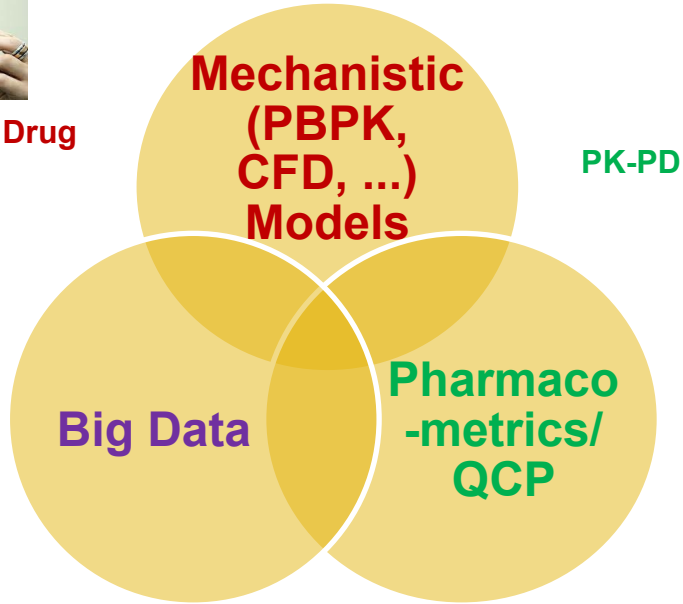


Non-Oral Drug

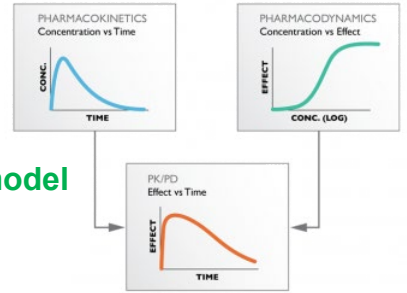
Oral Drug

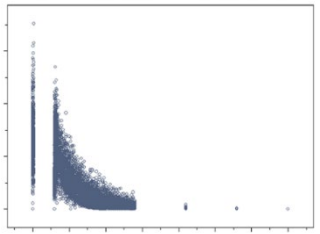


Machine learning toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models



PK-PD model





Population based model

fda.gov/cdersbia

Slide adapted from SBIA Presentation by Liang Zhao, Ph.D., MIE Industry Meeting Pilot Program for Generic Drugs: Introduction. 1/18/2024

Controlled Correspondence

- CC process provides a mechanism for timely feedback from FDA on a **particular element** of generic drug development
- *FDA Guidance for Industry: Controlled Correspondence Related to Generic Drug Development (March 2024)*
- This presentation focuses on CCs related to **clinical pharmacology topics**
- Requests more appropriately addressed through other mechanisms
  - Product development meeting (PDEV) request (i.e., pre-ANDA)
  - Model-integrated evidence (MIE) industry meeting

CC Classification and Timeline

- **Level 1 CC within 60 calendar days** of the submission date
- Level 1 CCs related to clinical pharmacology topics may include:
  - Guidance clarification related to in vivo BE studies
  - Special considerations related to in vivo BE studies

- **Level 2 CC within 120 calendar days** of the submission date
- Level 2 CCs related to clinical pharmacology topics may include:
  - Evaluations of alternative BE approaches
  - Evaluation of clinical content
  - Input from another office or center

Example of Level 1 and Level 2 CCs

Example of Level 1 CC

- Acceptability of reporting Cmax and a suitably truncated AUC (i.e., $AUC_{0\text{-}72hr}$) as primary endpoints for a BE study with pharmacokinetic (PK) endpoints for a long half-life drug
- Level 1 CC: Clarification of guidance and its application to this drug product

Example of Level 2 CC

- Acceptability of three-way, crossover design (i.e., a higher order design) to establish BE between the Test product versus U.S. reference listed drug (RLD) and the European reference product
  - Additional questions related to the statistical model
- Level 2 CC: Alternative BE study design; Multiple offices involved

Topics Related to Clinical Pharmacology

Category	Potential discussion topics
BE guidance questions and clarifications	• BE approach for highly variable drugs or NTI drugs • Suitability of AUC truncation • Assessment of steady-state attainment in PK studies
Study design and protocol development	PK sampling scheme and washout period
Statistical analysis and methods	• Covariate analysis in BE studies • Non-compartmental analysis (NCA) methods • Criteria for exclusion of data from analysis (e.g., statistical outliers) • Baseline correction methods and data analysis
Alternative BE metrics	Proposal of alternative partial AUC metrics
Alternative BE study designs	• Selection of alternative dose or study population • Adaptive design for BE studies that require a large number of subjects or present recruitment challenges (e.g., for orphan drugs, for ophthalmic drugs, for studies in sensitive patient populations) • Crossover design in patients without a washout period • Repeated crossover design to shorten study duration (e.g., for LAIs, for studies in sensitive patient populations)

Topics Related to PBPK Approaches

Oral Drug Products:

Category	Potential discussion topics
Support waiver of fed BE study for high-risk product	Using PBPK modeling to evaluate the impact of food on BE for high-risk products
Support waiver of BE study in subjects with gastric pH change	Using PBPK modeling to evaluate the impact of gastric pH on BE
Support BCS based biowaiver	PBPK modeling to evaluate the impact of excipients and API degradation on BE of Biopharmaceutical Classification System (BCS) Class III drug products and support BCS based biowaiver
Justify BE study design	• PBPK modeling to evaluate the impact of including single-sex subjects on BE • PBPK modeling to evaluate extrapolation of BE from adults to pediatrics or other special populations

Non-Oral Drug Products:

Category	Potential discussion topics
Mechanistic models for OIDPs	Validation plan of regional deposition models for OIDPs considering context of use and model impact
Mechanistic models for topical dermatological drug products	Validation plan of in vivo dermal PBPK and in silico IVPT models against the model context of use
LAI PBPK models	Development and validation plan for LAI PBPK models accounting for formulation attributes and interplay with local physiology to describe the in vivo API release
Model development vs. model validation	Appropriateness and selection of studies

Adaptive Design for BE Studies with PK Endpoints or Clinical Endpoints

- **Challenges with recruitment of an adequate number of patients** for a BE study with PK endpoint or clinical endpoints
- Applicants proposed various **adaptive designs** including sample size re-estimation at the interim analysis
- Recommendations on adaptive design are included in the revised *FDA Guidance for Industry, Statistical Approaches to Establishing Bioequivalence (December 2022)*
- In some CC requests, there was **insufficient information** to support the proposed adaptive design; or the proposed methods were **not appropriate** based on the study design and BE testing recommended in the PSG

Challenges with in vivo BE studies for long-acting injectables (LAI)

- Product-specific guidances (PSGs) for LAI products recommend a single-dose parallel PK study in cancer patients
- The required sample size for the study design recommended in the PSG is challenging for the cancer patient population
- Multiple inquiries received with proposed **alternative crossover designs**

Alternative PK Study Designs

- Single-dose, 2-way or fully-replicate, **crossover design in patients without a washout period**
- Crossover designs significantly reduce the required sample size, especially with a fully-replicate crossover design
- Drug release could extend beyond the dosing interval and impact estimation of AUC
  - Drug carryover may be different between Test product and Reference standard
- Approach should address concerns potential unequal carryover effects and its impact on BE assessment

Steady State PK Study with Repeated Crossover Design

- **Two consecutive PK measurements** taken for both Test product and Reference standard under steady-state conditions **(TTRR/RRTT)**
  - Shortens study length compared to conventional 4-way design (TRTR/RTRT) as the treatments only switch once
  - Design allows for widened BE limits using RSABE approach for HVD
- Alternative BE approach appears reasonable
  - Provide sufficient evidence to ensure absence of drug release beyond two dosing intervals

Zhang P, Donnelly M, Feng K, Gong Y, Liu X, and Babiskin A. *Assessment of Repeated Crossover Bioequivalence Design Under Steady State Conditions.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.

Zhang P, Donnelly M, Feng K, Gong Y, Liu X, Babiskin A, Yoon M, Zhao L, and Fang L. *Assessment of Repeated Crossover Bioequivalence Design Under Steady State Conditions*. Poster Presentation at the American Conference on Pharmacometrics (ACoP). National Harbor, MD, Nov. 06, 2023.

Recommended Practices

- Inquiry on acceptability of a PK study for a narrow therapeutic index (NTI) drug with alternative BE statistical criteria based on "outlier" data in a PK study

- An information request (IR) was sent to the applicant to provide additional data and clarifications, but no response was received within the requested timeframe
  - ***Provide all relevant data and information to address the CC request to avoid information requests from the Agency and potential delays***

- Follow-up CC request addressed the IR and proposed an additional question related to exclusion of “outlier” data in the statistical analysis
  - ***If possible, propose multiple questions related to a specific topic to avoid multiple CC requests***

MIE Pilot Program

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

Summary

- CC process is a mechanism to solicit feedback from FDA on a particular element of generic drug development
- Applicants are encouraged to submit CC requests with ***focused questions*** related to in vivo BE studies
  - Protocol development or evaluation of clinical studies (PK, PD, clinical endpoint)
  - Alternative BE approaches (e.g., study design, methods, assessment, etc.)
- Provide all relevant data and information to address the CC request to avoid information requests from the Agency and potential delays in response
- Certain requests may be more appropriately addressed through other mechanisms
  - Product development meeting request
  - MIE industry meeting

Closing Thought

Consider the CC process to solicit feedback from FDA on specific questions related to in vivo BE studies to facilitate generic drug development

Resources

- Controlled Correspondence Related to Generic Drug Development, Guidance for Industry, March 2024
- Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry, Guidance for Industry, October 2022
- Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, Guidance for Industry, August 2021
- Statistical Approaches to Establishing Bioequivalence, Guidance for Industry, December 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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U.S. FOOD & DRUG ADMINISTRATION

Questions?

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Questions about the program may be directed to genericdrugs@fda.hhs.gov


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