Model-Integrated Evidence for BE Assessment of Complex Generic Drugs

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 1: Cutting Edge Science

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Disclaimer

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

Learning Objective

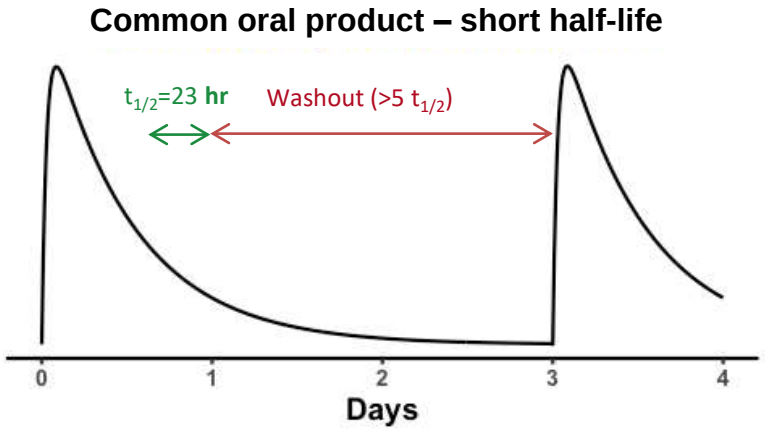
- Understand Background and Challenges in Long-Acting Injectable (LAI) Drug Products as an Example of Complex Generic Drugs
- Describe Model-Integrated Evidence (MIE) for Bioequivalence (BE) Assessment of Complex Generic Drugs
- Describe common deficiency in Pre-ANDA meeting packages applying MIE Approach for BE assessment of LAI Products

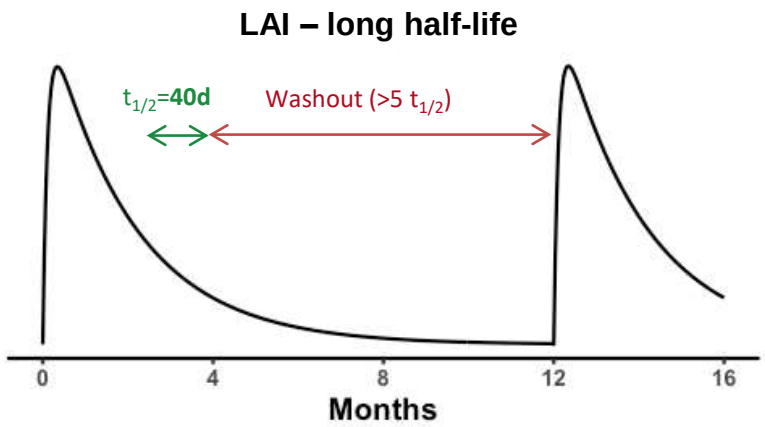
Long-Acting Injectable Drug Products

- LAI drug products are one class of complex generic drugs, formulated to achieve extended drug release action from days to years when administered via intramuscular (IM) and subcutaneous (SC) routes.

- These products can help improve patient compliance with a better therapeutic option to treat patients who adhere poorly to frequently administered medication.

Challenges in Bioequivalence Studies for LAI Products - Long half-life ($t_{1/2}$)





- Increased variation in PK parameters
- High drop out rate
- Not practical to perform a single-dose crossover BE study

Slide adapted from ACCP presentation by Mats Karlsson on 9/19/2019

Model Integrated Evidence

- **Model-informed drug development (MIDD)** under the Prescription Drug User Fee Amendments of 2017 (PDUFA VI)
  - To inform drug development and regulatory decision makings by using population pharmacokinetics (PPK), dose/exposure–response relationships, and biological and statistical models derived from preclinical and clinical data sources

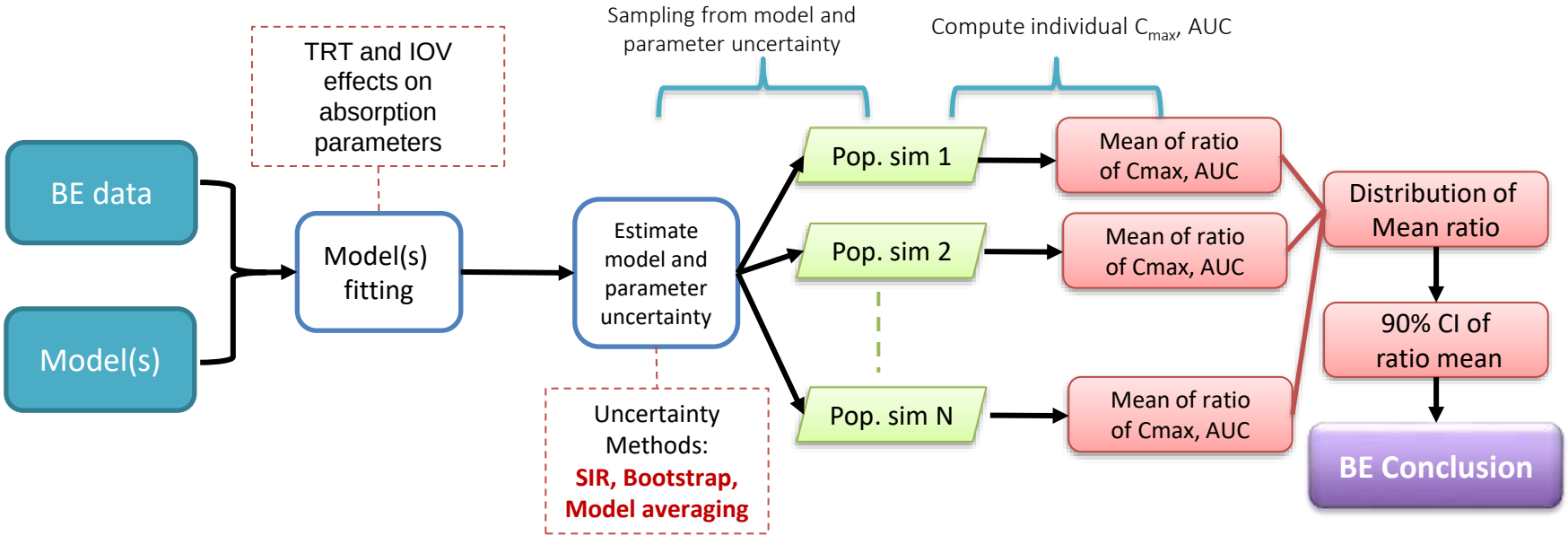
- **Model integrated evidence (MIE)** refers to using models not just to plan a pivotal study but to serve as pivotal evidence
  - Support product approval via a prespecified model-based analysis of an in vivo BE study
  - Support product approval via a virtual bioequivalence (VBE) study
  - In combination with relevant *in vitro* BE tests, support alternatives to otherwise recommended *in vivo* BE studies, including but not limited to PK, pharmacodynamics (PD), or comparative clinical endpoint BE studies

Slide courtesy: Dr. Liang Zhao

Clin Pharmacol Ther. 2019 Feb;105(2):338-349

Model-Integrated BE Method

Developed by Uppsala University



Modeling → Uncertainty estimation → Simulation → Conclusion

- ACOP 2019, Andrew Hooker, Development and comparison of model-based bioequivalence analysis methods on sparse data.
- ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.

Mats Karlsson (Uppsala University), Contract #: 75F40119C10018

Pre-ANDA Meeting Experience

- Several innovative approaches using MIE submitted by Generic Drug Industry for LAI products.
- Exchange of ideas between industry and FDA project team.
- Information request is common, takes time away from assessment clock.
- Clarify expectations from FDA.

Common Deficiencies

- Several innovative approaches using MIE submitted, common theme observed is lack of details.
  - **What** question related to BE will be addressed by MIE?
    - General questions such as ‘Modeling will be used to address a question during BE assessment’ lack necessary details for assessment.
  - **How** this question will be addressed by MIE?
    - Examples of details include, but not limited to, detailed plan, simulations to demonstrate to FDA how their plan will address the question etc.

Some Other Common Deficiencies

- Lack of Executive Summary in the submission.
- Model Codes for simulations are not submitted.

Challenge Question #1

Which of the following statements is NOT considered as good practices for a pre-ANDA meeting package with MIE?

A. Clearly identify the question that MIE approach will be used to answer.

B. Outline the scope of the question and what modeling exercise will be used to address those questions.

C. Provide a succinct executive summary.

D. State the objective of MIE approach as general as possible

Challenge Question #2

Which of the following statements is NOT considered as good practices for a pre-ANDA meeting package with MIE?

A. Include step by step guide on performing simulation and calculating PK metrics that is submitted in the study report.

B. Submit the code to perform simulations as presented in the study report including model codes or control streams and output listings from the simulations as well as the code to calculate the exposure metrics e.g., AUC, Cmax.

C. Assume there is no need to provide reference to the specific model code, simulation output in the study report.

D. Submit the summary of model codes files in the package.

Challenges for Applying MIE Approach

- Consensus on acceptable approaches for Model Validation for MIE?
- Different scenarios may need a different type/level of validation
  - What validation will be required if a new BE study is being proposed based on virtual simulation conducted using a population PK (PPK) model from a reference listed drug (RLD) (either one that is already published, or one that is updated with additional study data by a generic drug applicant)?
  - How can a published/modified PPK model from an RLD holder best be used to identify the most efficient study design for demonstrating BE?

Challenges for Applying MIE Approach

- Different scenarios may need a different type/level of validation
  - What validation will be needed for a BE study where the commonly recommended steady state is only partially conducted, e.g., 2-3 dose administrations, and the data from the limited clinical study is used to simulate steady state PK data, and a BE assessment is conducted on the simulated steady state PK BE data?
  - What if a different BE metric and/or limit is proposed that can ensure BE at steady state?
  - What validation will be required if the BE study is conducted in a limited number of subjects/patients (not adequately powered to demonstrate BE), but then the collected clinical data with the limited number of subjects is used to perform a virtual BE simulation with a higher number of subjects that provide adequate statistical power (e.g., 80%), and BE is assessed using this virtual BE dataset?

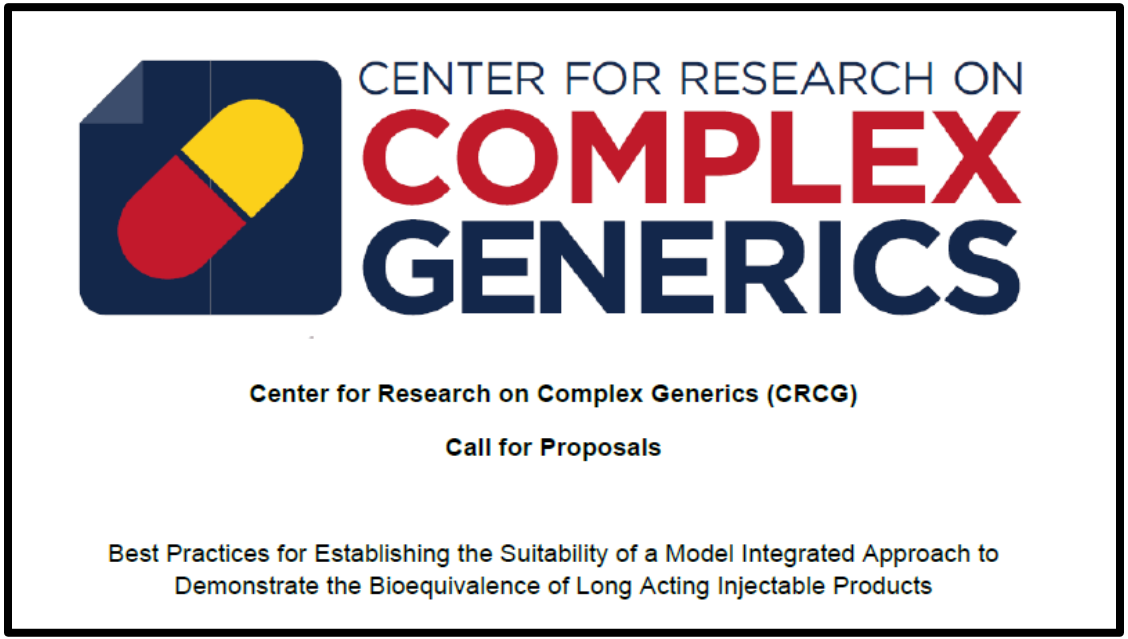
Challenges for Applying MIE Approach

- Proposing the pre-specified modeling analysis plan (MAP) that corresponds to the proposed model integrated BE study design.

- To determine which part of the MAP should be pre-specified, and where post-hoc analysis can and/or should be allowed.

A Public Virtual Workshop:

Best Practices for Establishing the Suitability of a Model Integrated Approach to Demonstrate the Bioequivalence of Long-Acting Injectable Products



Planned for November 30, 2021 in collaboration with Center for Research on Complex Generics (CRCG) http://www.complexgenerics.org/

Best Practices for Establishing the Suitability of a Model Integrated Approach to Demonstrate the Bioequivalence of Long-Acting Injectable Products

CRCG Call for Proposals Results

Congratulations to **Géraldine Ayral, Joel Owen and Clémence Pinaud at SimulationsPlus** (Lixoft and Cognigen divisions), and **Joga Gobburu at the University of Maryland School of Pharmacy** for initiating CRCG research projects on "Best Practices for Establishing the Suitability of a Model Integrated Approach to Demonstrate the Bioequivalence of Long Acting Injectable Products."

The awardees will

- present in a workshop planned for November 30, 2021.
- submit a detailed final report summarizing their study outcomes, which will be published in scientific journals.

In collaboration with Center for Research on Complex Generics (CRCG)
http://www.complexgenerics.org/

Summary

- Development of Long-Acting Injectable Products is often challenging.
- Model-Integrated Evidence approach can save time and resources in development of Long-Acting Injectable Products.
- Pre-ANDA meeting submission applying best practices can increase assessment efficiency and efficient generic drug development.
- FDA welcomes innovative alternative approaches to demonstrate bioequivalence.

Thank You!

- Alternative approaches to demonstrate bioequivalence: Applicants can submit their proposal through FDA's Pre-ANDA program.
  - Pre-ANDA Program Information
  - Guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Nov. 2020)
  - For questions about submitting Pre-ANDA meeting requests for complex generic drug products online please contact PreANDAHelp@fda.hhs.gov

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FDA U.S. FOOD & DRUG ADMINISTRATION

Questions?

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