Considerations of Bioequivalence Studies for Long-Acting Injectables and the Application of Model-Integrated Evidence Approaches

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Disclaimer

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Outline

- Considerations of bioequivalence (BE) studies for generic long-acting injectables (LAIs)
- Example product-specific guidances (PSGs) on complex LAIs
- Opportunities with model-integrated evidence (MIE) approaches
- Regulatory considerations for using MIE

Long-Acting Injectables (LAIs)

- LAIs are drug products that are designed to provide controlled/sustained release for days to months.
- The benefits of reduced administration frequency are particularly impactful to patients with chronic conditions (e.g., antipsychotic drugs, hormonal contraceptives, cancer drugs, etc.).

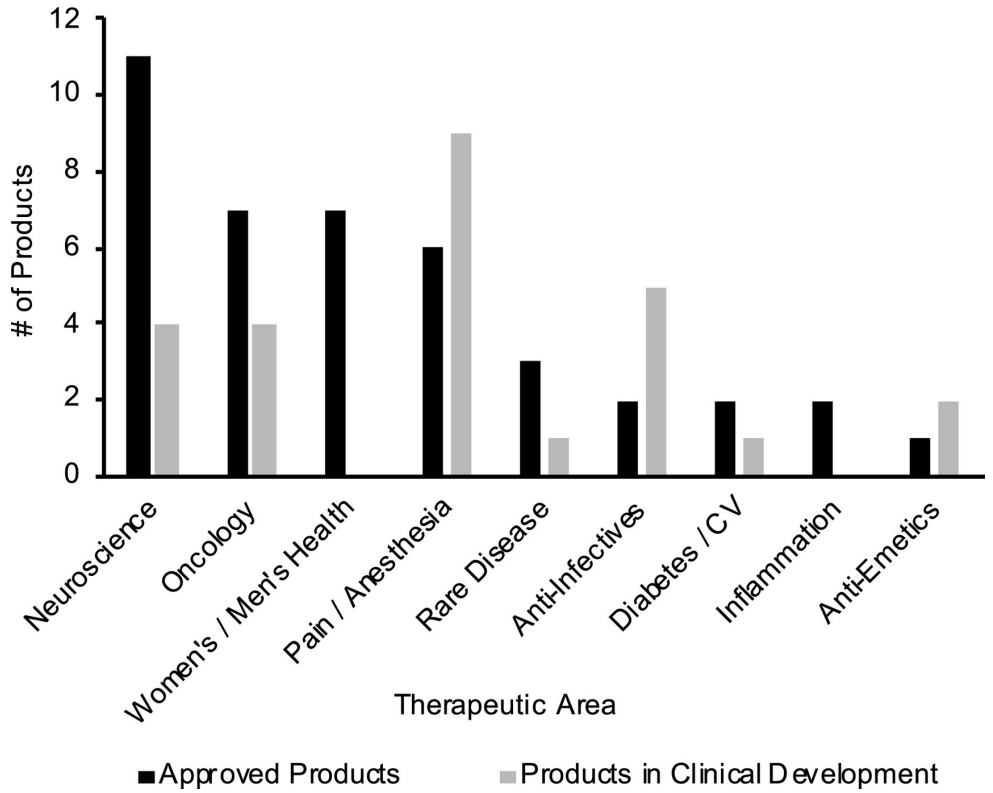


Fig. 1. Number of LAI products that have been approved by the U.S. FDA via an NDA pathway (*N* = 41) or that are in clinical development as of May 2021 (*N* = 26).

M.N. O'Brien et al., Challenges and opportunities in the development of complex generic long-acting injectable drug products, Journal of Controlled Release 336 (2021) 144-158

Main Types of LAI Products

Non-complex LAIs

- **Oily solutions** e.g., fulvestrant intramuscular (IM) solution

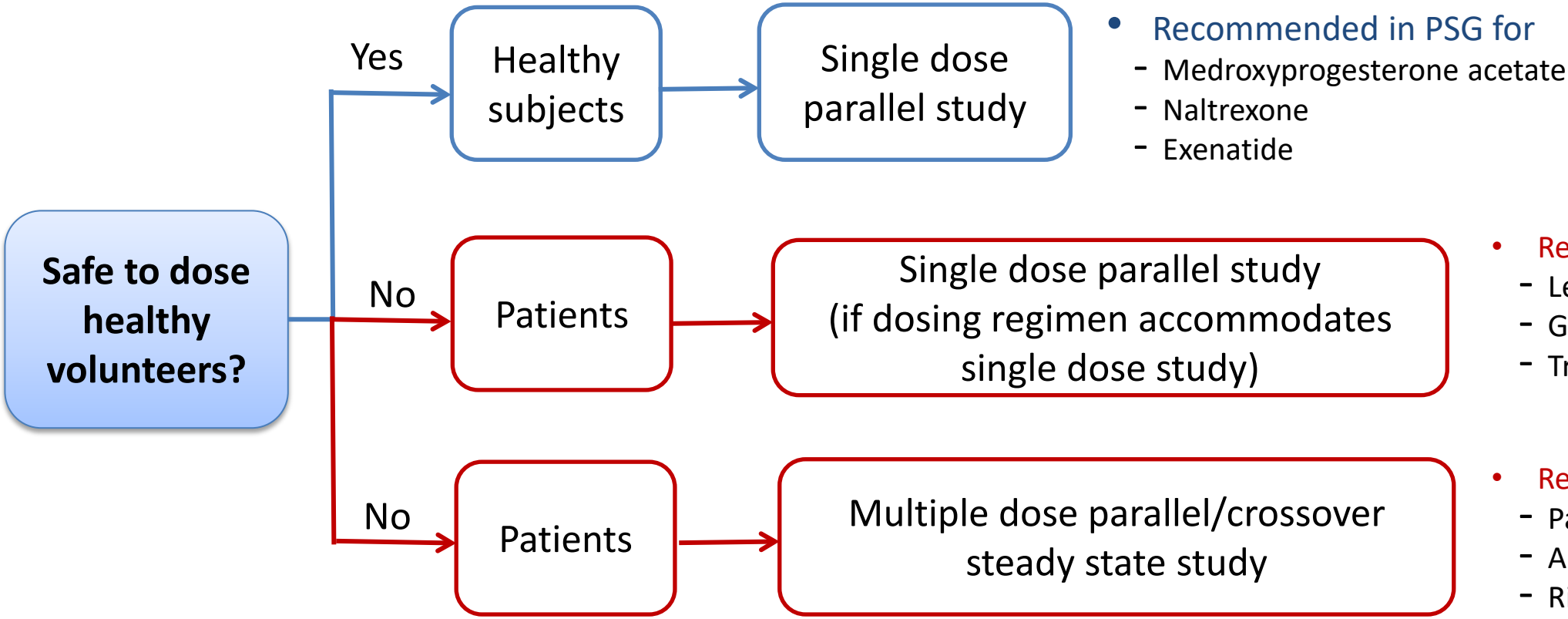
- In vivo BE study is waived under 21 CFR 320.22(b)(1).
- Generic approval based on qualitatively (Q1) and quantitatively (Q2) the same for the inactive ingredients.

Complex LAIs (non-solution)

- **Drug substance suspensions** e.g., paliperidone palmitate IM injection, medroxyprogesterone acetate IM injection
- **Polymer microspheres** e.g., leuprolide acetate depot injection, risperidone IM injection.
- **In situ forming polymer implants** e.g., leuprolide acetate subcutaneous (SC) power
- **Multivesicular (or other) liposomes** e.g., bupivacaine liposomal injectable injection

- For parenteral drug product, a generic drug must be Q1/Q2 the same as the RLD.
- In general, in vivo BE study is needed for complex LAIs, in vitro BE option is available only for certain product.

Pharmacokinetics (PK) BE Studies Recommended for LAI Products in Product-Specific Guidance (PSG)



- Recommended in PSG for
  - Medroxyprogesterone acetate
  - Naltrexone
  - Exenatide

- Recommended in PSG for
  - Leuprolide acetate
  - Goserelin acetate
  - Triptorelin pamoate

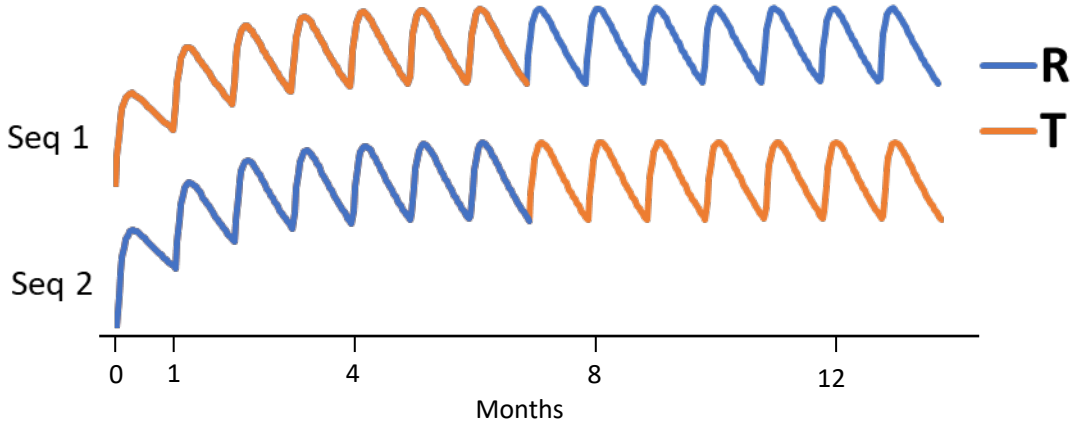
- Recommended in PSG for
  - Paliperidone palmitate
  - Aripiprazole
  - Risperidone

Partial AUC is recommended in single dose study for certain LAI products based on considerations on clinical relevance/formulation characteristics.

Challenges in PK BE Studies for Generic LAIs

- For most LAIs, there are no approved generics to date.
- Due to the long-acting nature of LAIs, in vivo BE studies can last for several months or even years.
  - Long study duration
  - High variability/large sample size
    - Parallel study design, multiple clinical centers, etc.
  - Recruiting difficulty
    - BE studies often need to be conducted in patients for safety concerns
  - High dropout

Single-dose crossover BE study – not practical



Steady state crossover BE study – long study duration

PSG for Cabotegravir; Rilpivirine

Recommended Feb 2023

Active Ingredients: Cabotegravir; Rilpivirine

Dosage Form; Route: Suspension, extended release; intramuscular

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, parallel, in vivo
   Strength: Cabotegravir 600 mg/3 mL, rilpivirine 900 mg/3 mL
   Subjects: Male and nonpregnant, non-lactating females, general population.
   Additional comments: Prior to injection of extended-release injectable suspensions, an optional oral lead-in dosing followed by a washout period may be considered to assess the tolerability of cabotegravir and rilpivirine as described in the product label.

Analytes to measure: Cabotegravir in plasma; rilpivirine in plasma

Bioequivalence based on (90% CI): Cabotegravir; rilpivirine

Waiver request of in vivo testing: 400 mg cabotegravir, 600 mg rilpivirine based on (i) acceptable bioequivalence study on the 600 mg cabotegravir, 900 mg rilpivirine strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- **Drug substance suspension:** the product's long-acting feature is based on the extremely low aqueous solubility of each drug substance and slow diffusion at intramuscular site of injection.
- The drug product exhibited flip-flop kinetics with prolonged apparent terminal half-lives (half-life of cabotegravir is 5.6-11.5 weeks, half-life of rilpivirine is 13-28 weeks).
- PK sampling may extend > 1 year to capture the complete PK profile.
- No approved generic drugs.

FDA's PSG for Generic Drug Development available at:
https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

PSG for Paliperidone Palmitate

Recommended Aug 2021

Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Suspension, extended release; intramuscular

Recommended Study: One study

1. Type of study: Bioequivalence (BE) study with Pharmacokinetic (PK) endpoints
   Design: Parallel or crossover steady state
   Strengths: 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, 819 mg/2.625 mL
   Subjects: Male and nonpregnant female patients with schizophrenia who are already receiving a stable regimen of 3-month paliperidone palmitate extended-release suspension via the intramuscular route. Patients who are already receiving any dosage regimen of 3-month paliperidone palmitate injection every three months would be eligible to participate in the study by continuing their established maintenance dose.

Analyte to measure: Paliperidone in plasma

Bioequivalence based on (90% CI): Paliperidone

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and C_{max}) should be within 80% - 125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The trough concentration data should also be analyzed to verify that steady-state was achieved prior to pharmacokinetic sampling.

- **Drug substance suspension**
- Steady state study is challenging for paliperidone IM injections that are administered every 3 months or every 6 months as steady state may take 1-3 years to achieve.

PSG for Leuprolide Acetate

Recommended May 2010; Revised Feb 2014, Aug 2021

Active Ingredient: Leuprolide acetate

Dosage Form; Route: Injectable; injection

Recommended Study: One study

1. Type of study: In vivo
   Design: Randomized, single dose, parallel
   Strength: 7.5 mg/vial
   Subjects: Prostatic carcinoma patients undergoing initial therapy or receiving a stable regimen of leuprolide acetate (7.5 mg/vial) via intramuscular injection route.

Analyte to measure: Leuprolide in plasma

Bioequivalence based on (90% CI): Leuprolide

The 90% confidence intervals of the following pharmacokinetic (PK) parameters should meet the acceptable limits of [80.00-125.00]: Log-transformed $AUC_{7\text{-}t}$, $AUC_{0\text{-}t}$, and C_{max}, where $AUC_{7\text{-}t}$ is the area under the plasma-concentration vs. time curve from Day 7 to the last sampling time point, $AUC_{0\text{-}t}$ is the area under the curve from 0 to the last sampling time point, and C_{max} is the maximum plasma concentration. Note that the last sampling time point 't' equals the dosing interval of the product used in the in vivo PK study.

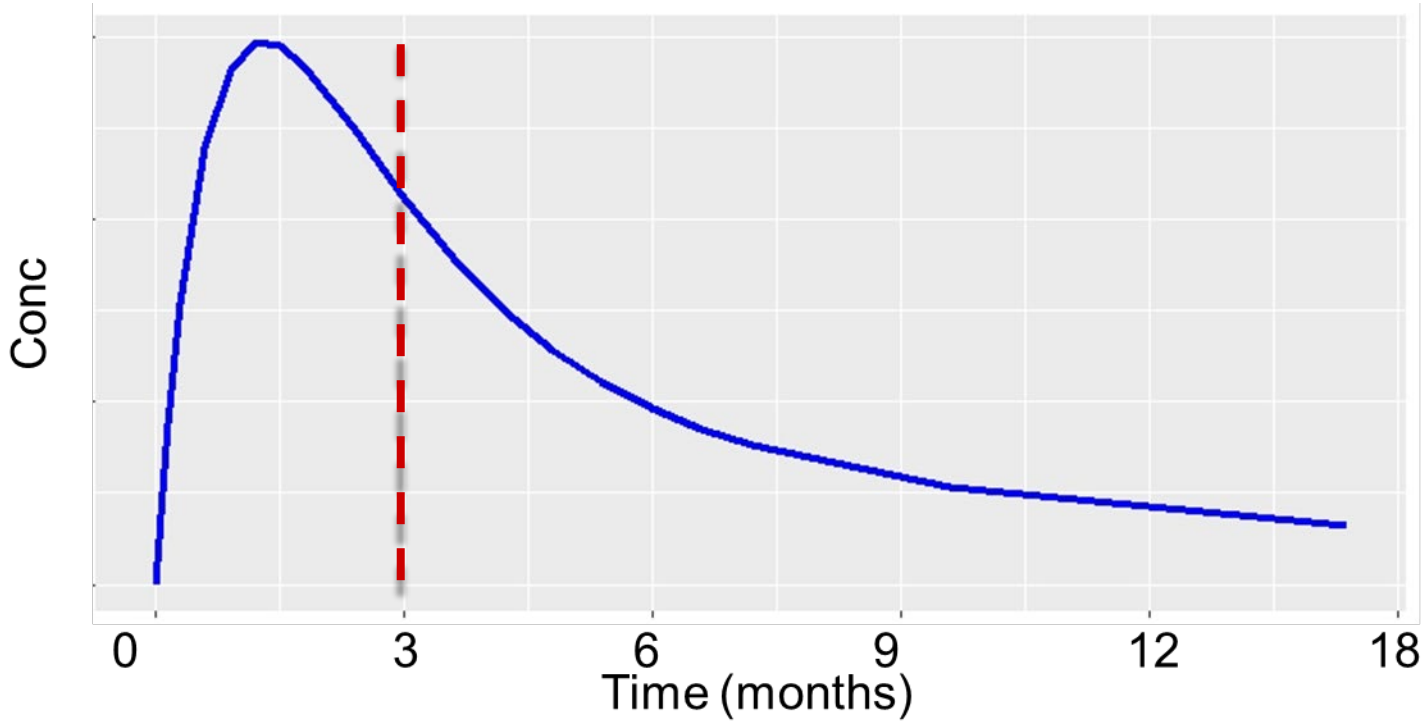
In addition, for prostatic carcinoma patients undergoing initial therapy, after the PK study is completed, the treatment should not be discontinued or delayed for a second dose.

- **Polymer microspheres:** leuprolide microsphere-based formulations in general exhibit PK profiles with a very high burst release shortly after injection (e.g., within a week after injection) followed by a steady, sustained drug concentrations.
- The sustained release part of this drug's PK profile is driven by drug release from microspheres. Partial AUC (AUC7-t) is recommended to ensure comparable sustained release for the test product and the RLD.
- The parallel study requires a large sample size (e.g., > 400).
- The required sample size is challenging for the target prostatic cancer patient population.
- No approved generic drugs.

Opportunities for Model-integrated Evidence (MIE) in Generic LAI Development

- Enhance the efficiency of PK BE studies: alternative designs with shorter study duration and/or smaller sample size supported by modeling
  - Early truncation of single dose PK study -> shorter study duration
  - Non-steady state study -> shorter study duration
  - Carryover adjustment to allow crossover design with incomplete washout -> smaller sample size compared to parallel design
- Mechanistic in vitro-in vivo correlation (IVIVC) modeling to support risk assessment of deviations in *in vitro* characterizations.
- Physiologically based PK (PBPK) modeling informed by *in vitro* characterization data and a small-scale in vivo PK study to reduce the recruiting burden.
- We see a clear demand: increased use of modeling approaches in pre-abbreviated new drug application (pre-ANDA) interactions and ANDA submissions.

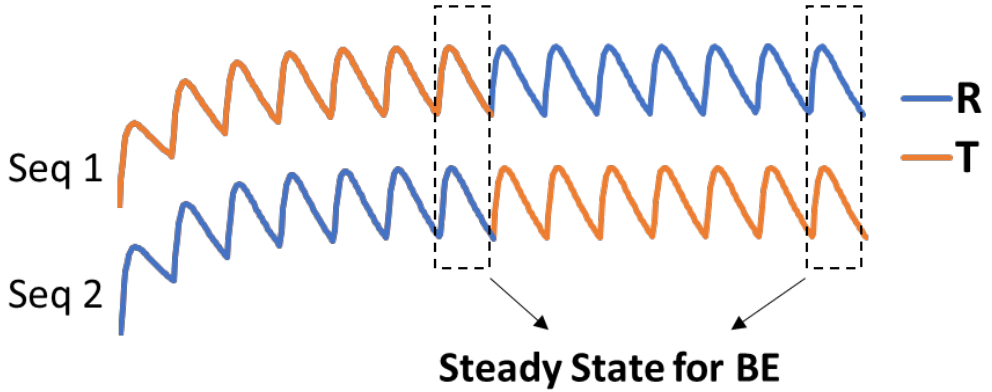
Example 1 - Early Truncation of Single Dose PK Study



- Use modeling to explore a feasible early truncation.
- Use modeling to evaluate the risk associated with not assessing PK beyond the truncation timepoint and the impact on BE assessment.

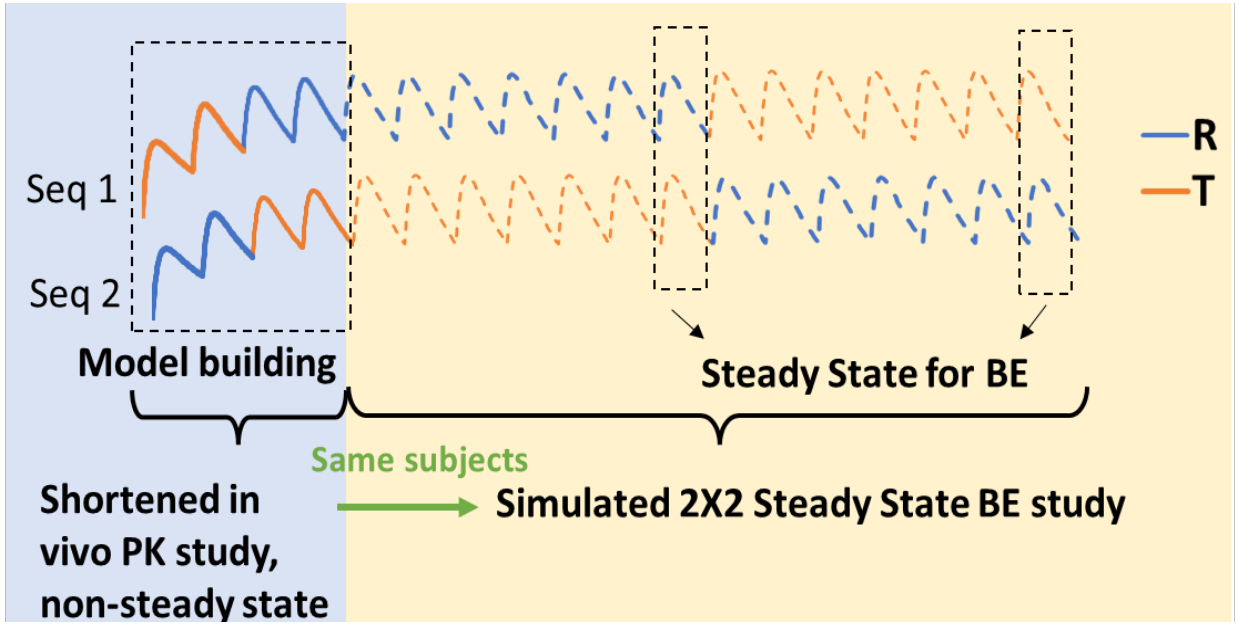
Example 2 – Assess BE at Non-Steady State

Conventional 2X2 Crossover Steady State PK BE Study

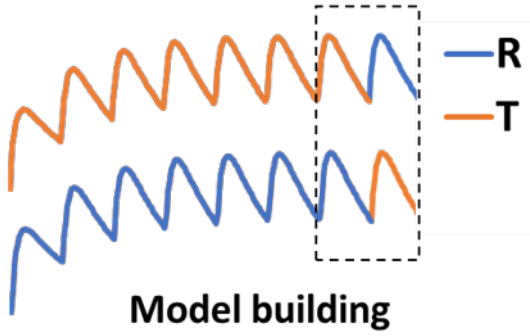


- Significantly shorten the study duration by assessing BE at non-steady state.

Example 1. Continuation of "in silico" dosing to steady state



Example 2. Switch design

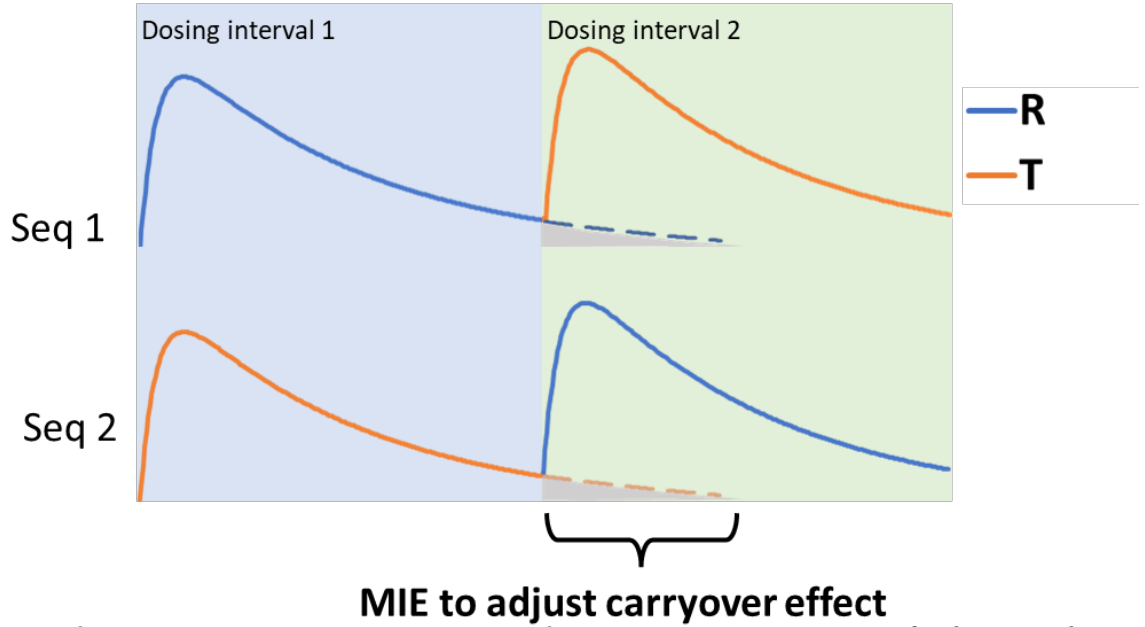


Modeling is used to separate the superposition of the test and reference products after switch, and then perform a model-based BE analysis

Example 3 - MIE to Support Alternative Crossover Design

Alternative crossover BE study

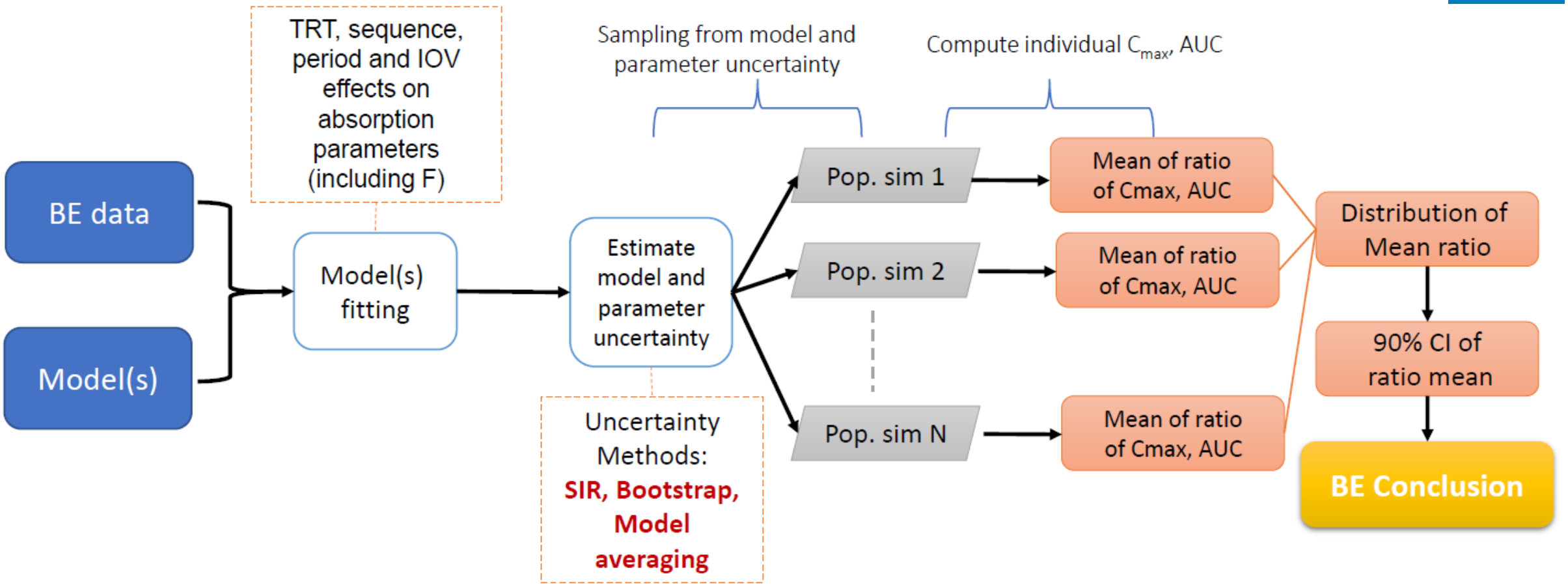
No washout per dosing regimen



- In some cases, steady state crossover study in patients can't be achieved either due to irregular dosing frequency or length of treatment.
- Adjusting carryover in a crossover study when the washout is not feasible – removing carryover via population PK modeling
  - Do not disturb patients' dosing regimen
  - Allow crossover BE comparison with smaller sample size (compared to a parallel study)

Example 4 – MIE BE Framework

(Developed by Uppsala University Research Team (Andrew Hooker & Mats Karlsson))



Slide adapted from FDA-CRCG Workshop Presentation by Andrew Hooker, Model Integrated Methods and Innovative Study Designs for Generic LAI Product Development and Regulatory Assessment, 11/30/2021.

Potential Applications of the Developed MIE Framework

- BE evaluation for highly variable drugs with an incomplete washout design (FDA contract: 75F40122C00139)
  - *Huang Z, et al. Model-Integrated Bioequivalence Method for Highly Variable Drugs with Long Half-Life: a Simulation Study Comparing Complete Washout and Incomplete Washout Designs. Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. Rome, Italy, Jun. 26, 2024.*
- BE evaluation with sparse data (FDA contract: HHSF223201710015C)
  - *Chen X, Nyberg HB, Donnelly M, Zhao L, Fang L, Karlsson MO, Hooker AC. Development and comparison of model-integrated evidence approaches for bioequivalence studies with pharmacokinetic end points. CPT Pharmacometrics Syst Pharmacol. 2024 Aug 23. doi: 10.1002/psp4.13216. Epub ahead of print. PMID: 39177211.*
  - *Bjugård Nyberg H, Chen X, Donnelly M, Fang L, Zhao L, Karlsson MO, Hooker AC. Evaluation of model-integrated evidence approaches for pharmacokinetic bioequivalence studies using model averaging methods. CPT Pharmacometrics Syst Pharmacol. 2024; 00: 1-14. doi:10.1002/psp4.13217*
- BE evaluation at non-steady state PK (e.g., switch design) (FDA contract: 75F40119C10018)
  - *Gong Y, Zhang P, Yoon M, et al. Establishing the suitability of model-integrated evidence to demonstrate bioequivalence for long-acting injectable and implantable drug products: Summary of workshop. CPT Pharmacometrics Syst Pharmacol. 2023; 12: 624-630. doi:10.1002/psp4.12931*

Regulatory Considerations of Using MIE

- Meeting regulatory standards to generate BE evidence
  - How to ensure unbiased equivalence determination for formulation differences assessment?
  - How to characterize the uncertainty and propose an appropriate BE statistical method?
- Sufficient verification and validation
  - What would be the appropriate model validation strategy? Additional model validation strategies may be needed using more quantitative measures beyond the general predictive/diagnostics checks.
  - How much prior data are needed to propose and evaluate an MIE approach?
- The model development and validation process and criteria should be pre-specified.
  - Using MIE approach in BE assessment should not be interpreted as post-hoc analyses that may lead biased BE results.
- Best practice of MIE approach in regulatory submission (MIE Pilot Program)
- Standardization of model sharing, submission, communication (Model Master File)

MIE Industry Meeting 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

Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants

MIE Pilot Program General Principles document

Summary and Resources

- FDA continues to improve PSGs based on updated understanding obtained through communications with generic industry (via public workshop, pre-ANDA interactions) and Generic Drug User Fee Amendments (GDUFA) funded research.
  - PSG Database
  - FY 2024 GDUFA Science and Research Report
  - Educational events and workshops hosted by FDA and Center for Research on Complex Generics (CRCG)
- Generic applicants are encouraged to develop alternative BE approach (e.g., alternative design supported by MIE) and engage with the Agency early during development.
- **Contacts:**
  - Pre-ANDA Meetings Program for Complex Generic Products. For questions about submitting Pre-ANDA meeting requests, please contact PreANDAHelp@fda.hhs.gov.
  - Specific questions regarding the MIE approaches can be submitted to the MIE Pilot Program. Questions about the program may be directed to MIE@fda.hhs.gov.

ANDA: abbreviated new drug application

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- FDA/CRCG Workshop: Considerations and Potential Regulatory Applications for a Model Master File (May 2-3, 2024): https://www.fda.gov/drugs/news-events-human-drugs/fdacrcg-workshop-considerations-and-potential-regulatory-applications-model-master-file-05022024#event-information


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