Strategic Development of Generic Long-Acting Injectables: Model-Integrated Evidence Approaches

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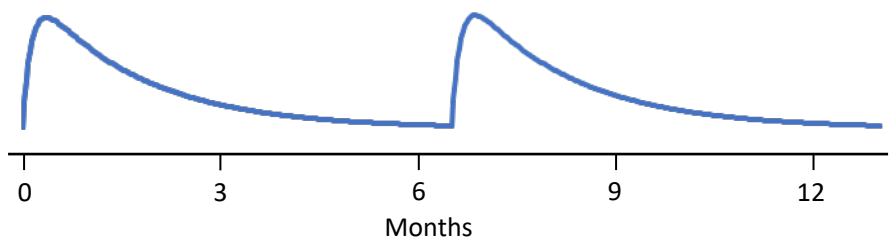
Outline

- Challenges in bioequivalence (BE) studies for generic long-acting injectables (LAIs)
- Opportunities with model-integrated evidence (MIE) approaches
- Regulatory considerations for using MIE
- Looking into the future

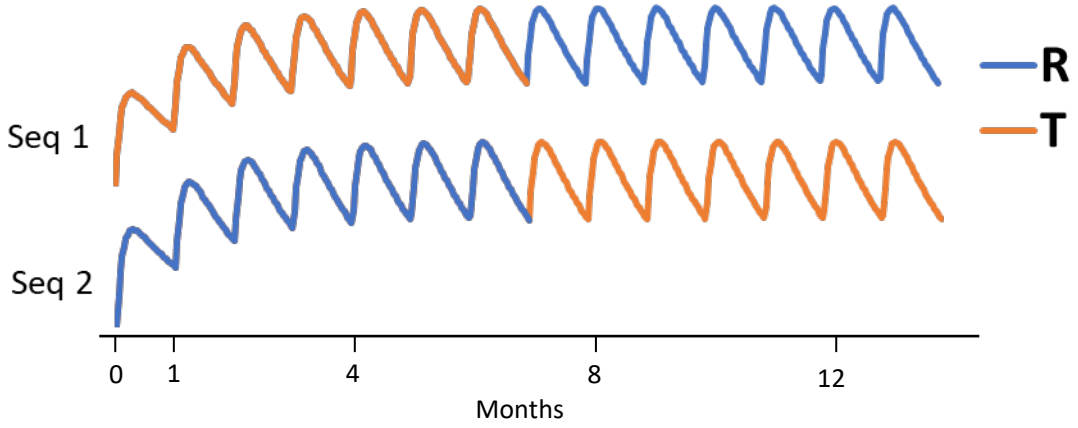
Challenges in BE Studies for Generic LAIs

- For most LAIs, there is no generic approval 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, demographics, etc.
  - Recruiting difficulty
    - BE studies often need to be conducted in patients for safety concerns
  - High dropout

LAI: long half life, long washout

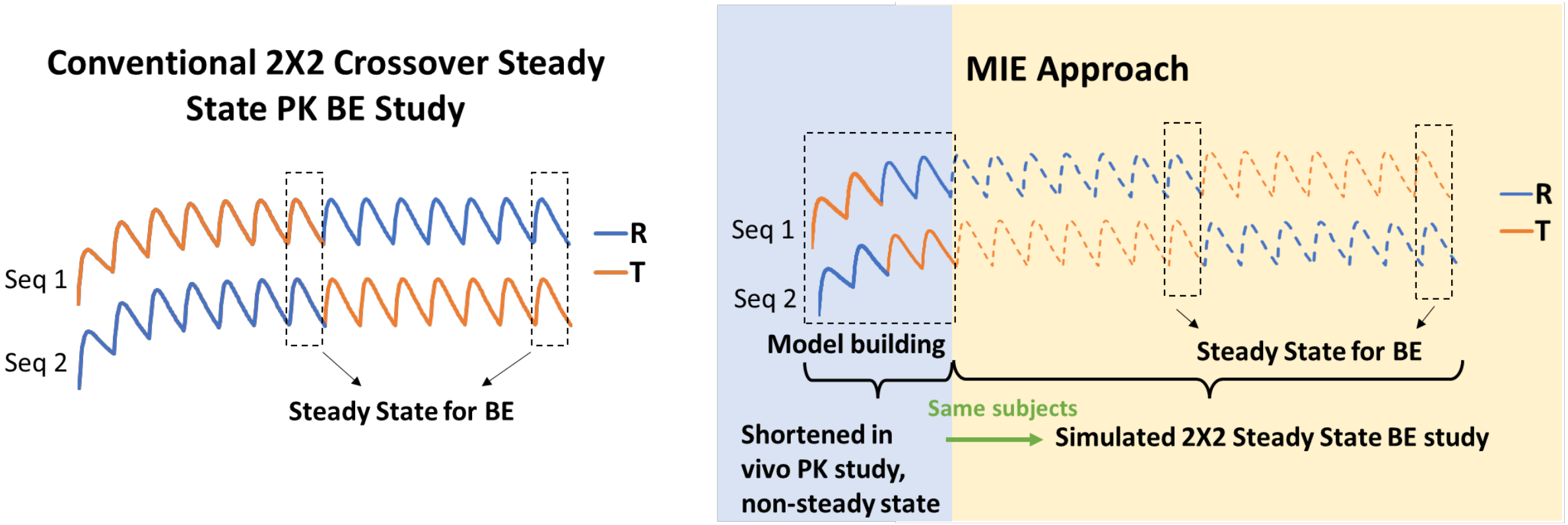


Single-dose crossover BE study – not practical



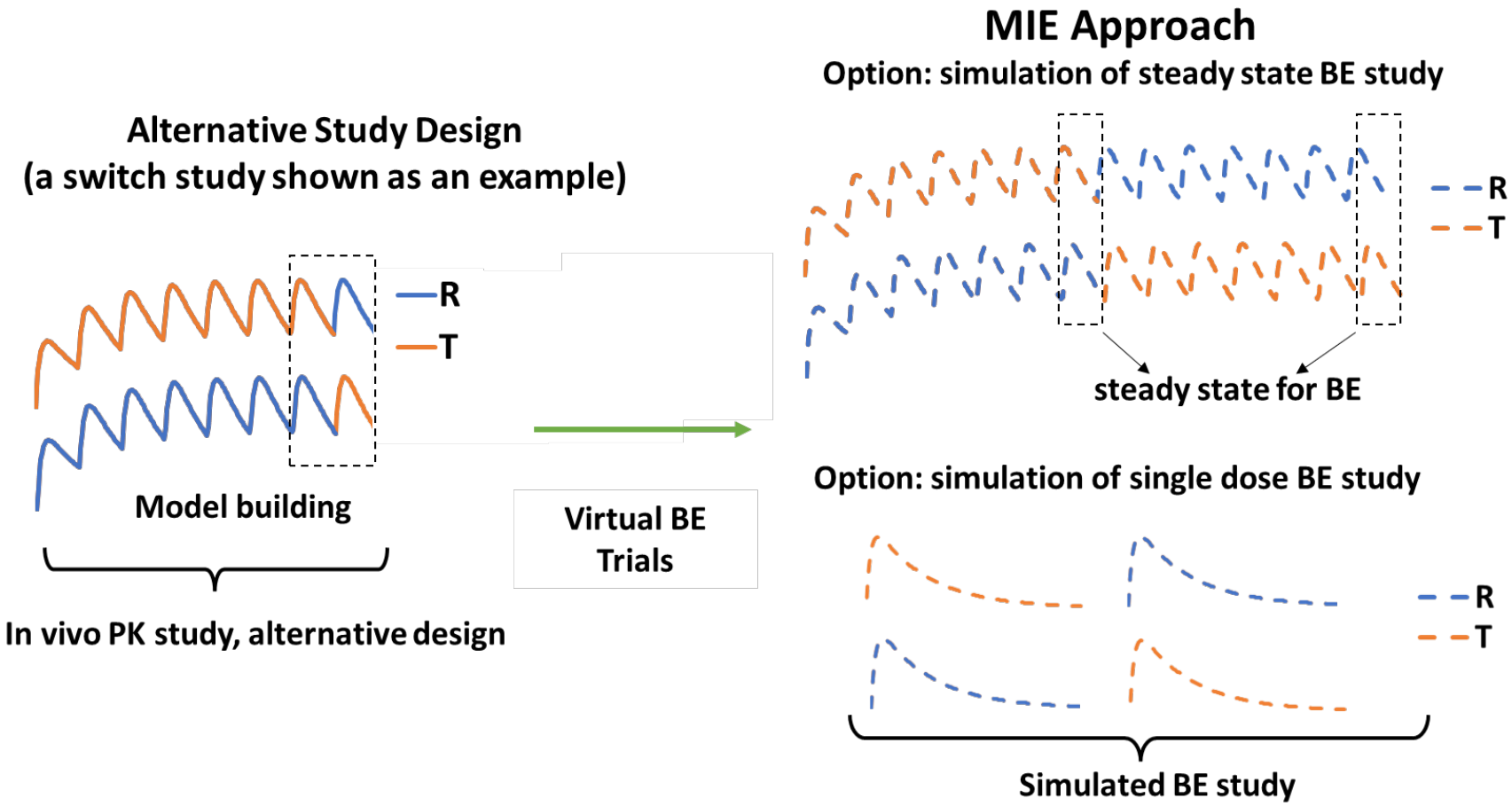
Steady state crossover BE study – long study duration

MIE: “in silico” Dosing to Steady State



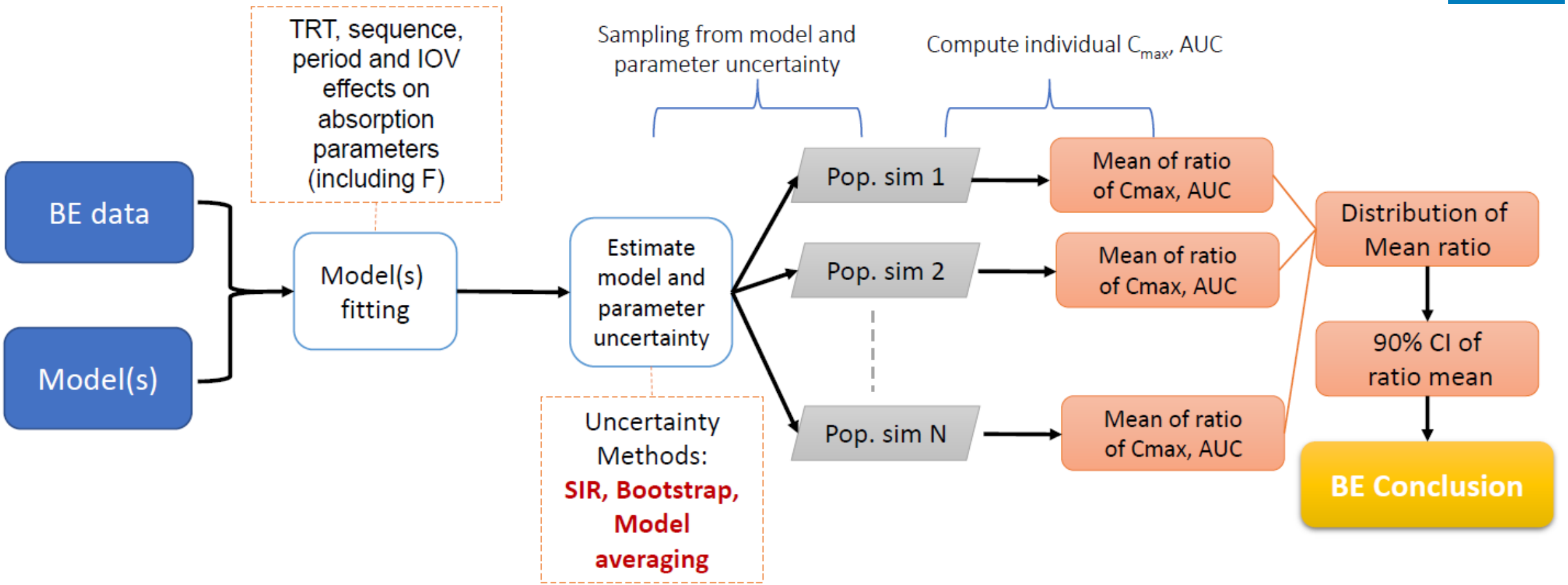
- Can be used for LAI that recommends a steady state BE study in patient population such as LAI antipsychotics: paliperidone palmitate, aripiprazole, etc.
  - Shorten study duration
  - Allow crossover BE comparison with smaller sample size (compared to a parallel study)

MIE: Virtual BE Trials



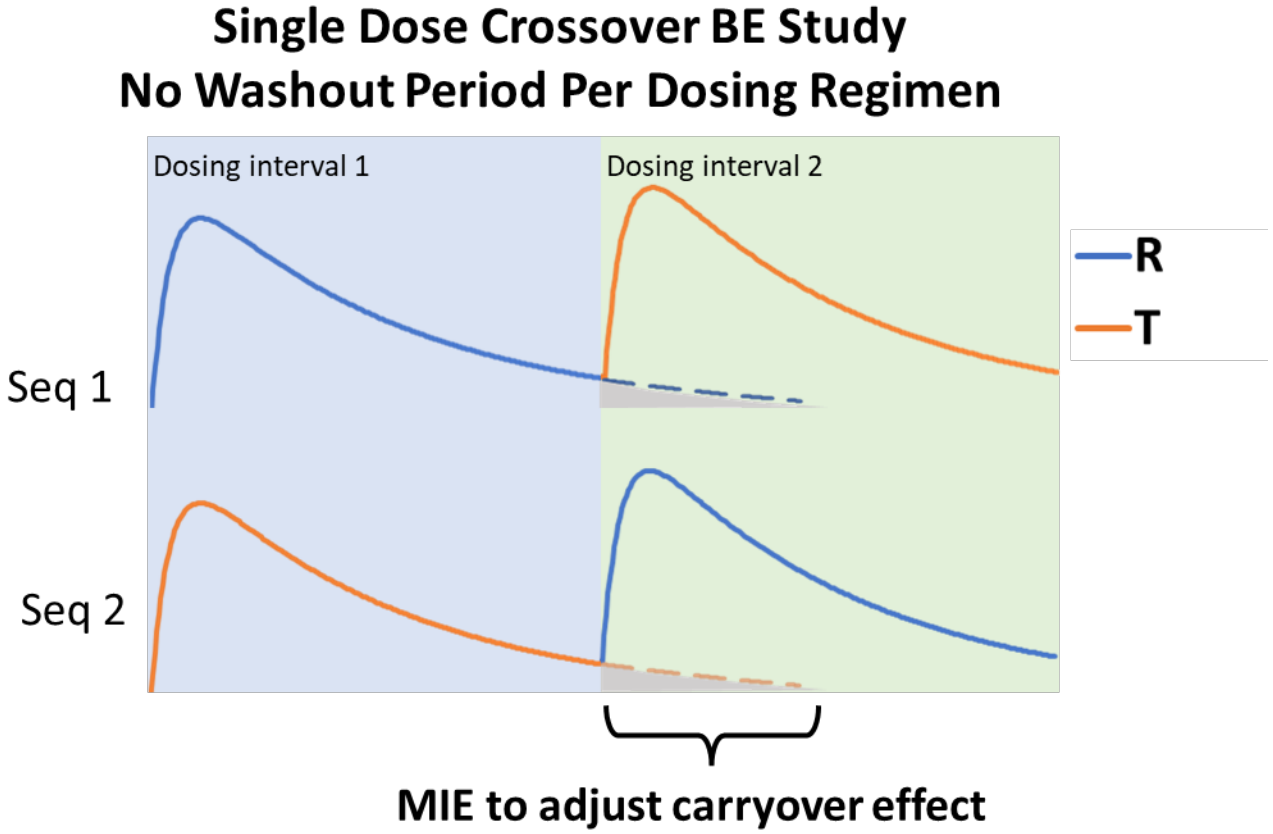
- Allow more flexibility in clinical study design
  - Simulate additional subjects
  - Simulate different virtual BE trials

Example Virtual BE Framework



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.

MIE: Adjusting Carryover



- Can be used for LAI that recommends a single dose parallel BE study in patient population such as LAI gonadotropin-releasing hormone (GnRH) agonist: leuprolide acetate
  - Do not disturb patients' dosing regimen
  - Allow crossover BE comparison with smaller sample size (compared to a parallel study)

Regulatory Considerations for Using MIE

- Meeting regulatory standards to generate BE evidence
  - How to detect the formulation differences that would not lead to biased equivalence determination?
  - 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.

Increased Global Collaboration

- Parallel scientific advice (PSA) pilot program between FDA and European Medicines Agency (EMA) for complex generic/hybrid products
  - Allows prospective applicants to engage in concurrent scientific conversation with both agencies
  - Increases dialogue between the two agencies
  - Optimizes the applicant's global product development program by enabling them to discuss specific questions concurrently with both agencies
  - Drives convergency to help applicants avoid redundant replication of work and unnecessary testing replication or unnecessary diverse testing methodologies
  - An opportunity to expand the number of generic drug applicants that submit applications to both agencies

https://www.fda.gov/drugs/generic-drugs/fda-ema-parallel-scientific-advice-pilot-program-complex-generichybrid-products

Examples of Good Candidates for PSA Meetings

- Proposals for a single BE study that may satisfy both agencies, especially when FDA and EMA have different recommendations in their respective product-specific guidances
- Proposals for scientific approaches with data/information to support the use of a common comparator in BE studies that are acceptable to both agencies
- Proposals to use modeling and simulation to improve efficiency of the development program

https://www.fda.gov/drugs/our-perspective/cders-ogd-and-emas-parallel-scientific-advice-pilot-program-complex-generics-works-increase

Looking Into the Future

- Global acceptance of MIE approach
- Best practice of MIE approach in regulatory submission
- Standardization of model sharing, submission, communication
  - Model Master File (*FDA/CRCG Workshop, May 2-3, 2024)*

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