Considerations and Challenges of Pharmacokinetics Bioequivalence Studies for LAIs and the Application of Model-Integrated Evidence (MIE) Approaches

GBHI 2024 Session 2

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Disclaimer

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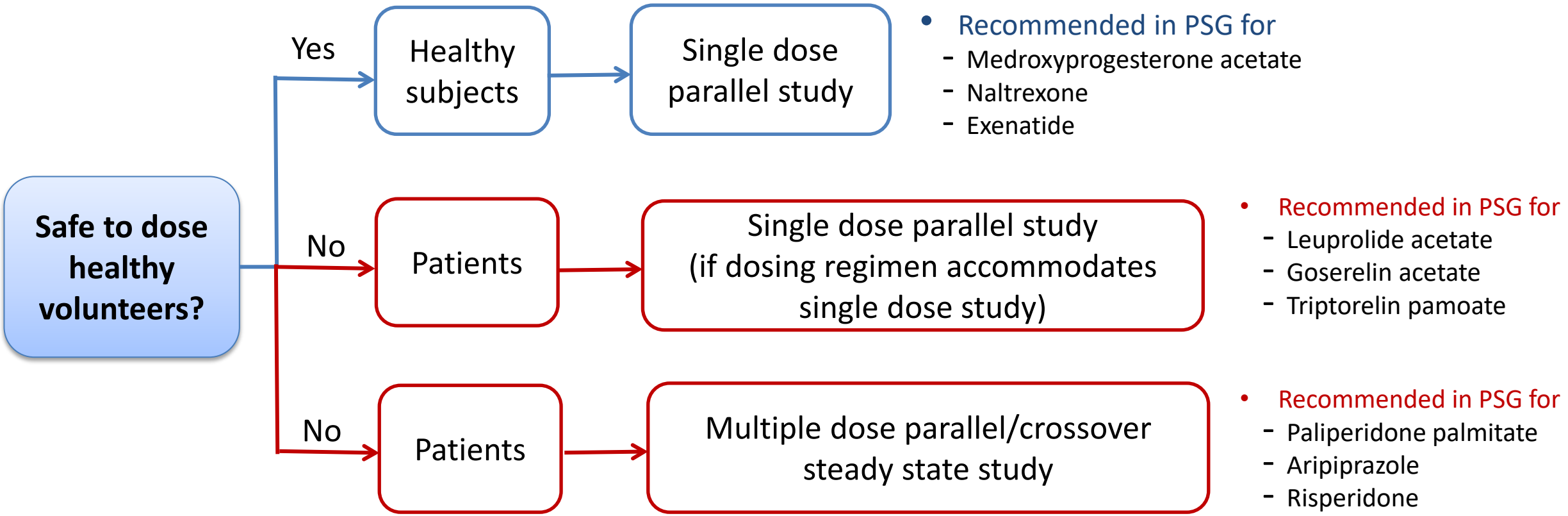
Outline

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

FDA Recommended BE Studies for LAI Products



- 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

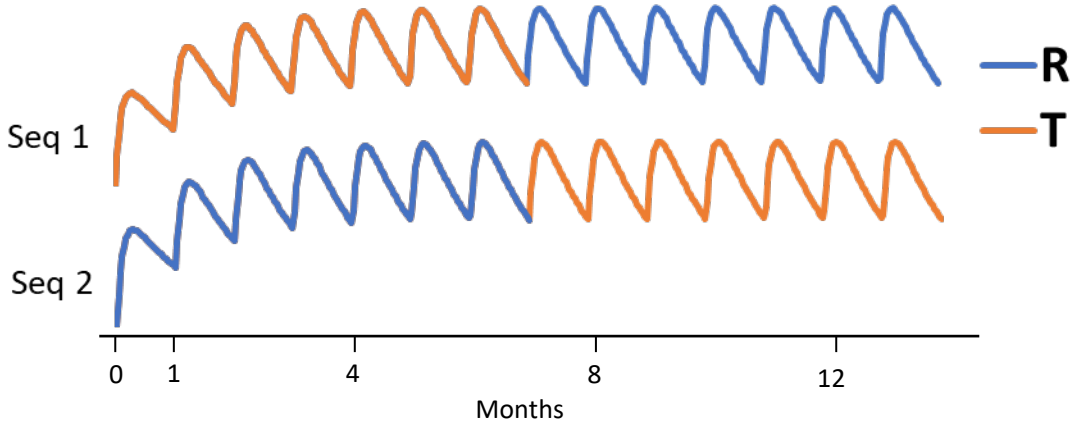
Partial AUC is recommended in single dose study for certain LAI products based on considerations on clinical relevance/formulation characteristics (see Day 2 presentation from Lucy Fang, FDA for detailed discussion)

PSG: product-specific guidance

Challenges in 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, demographics, etc.
  - Recruiting difficulty
    - BE studies often need to be conducted in patients for safety concerns
  - High dropout

Single-dose crossover BE study – not practical

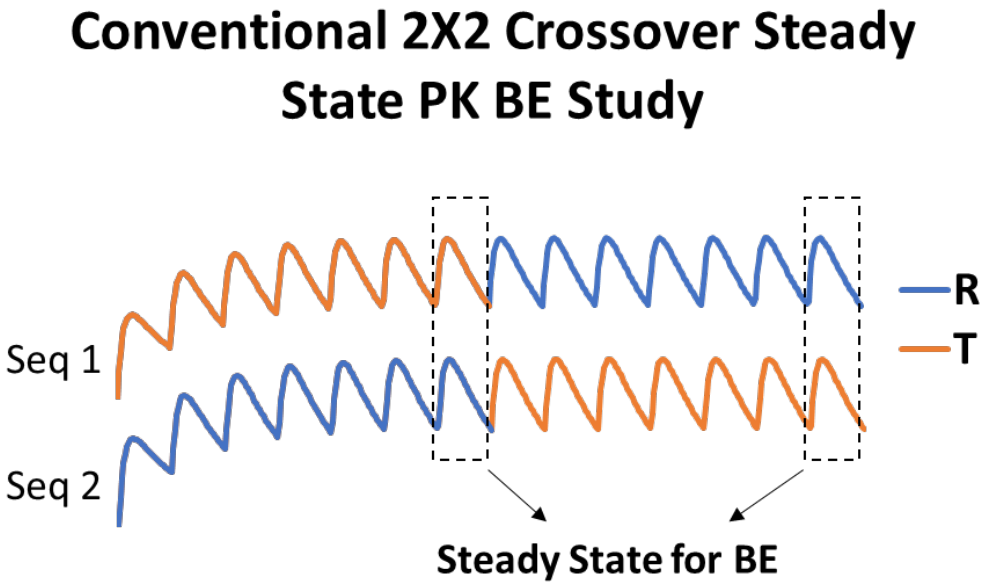


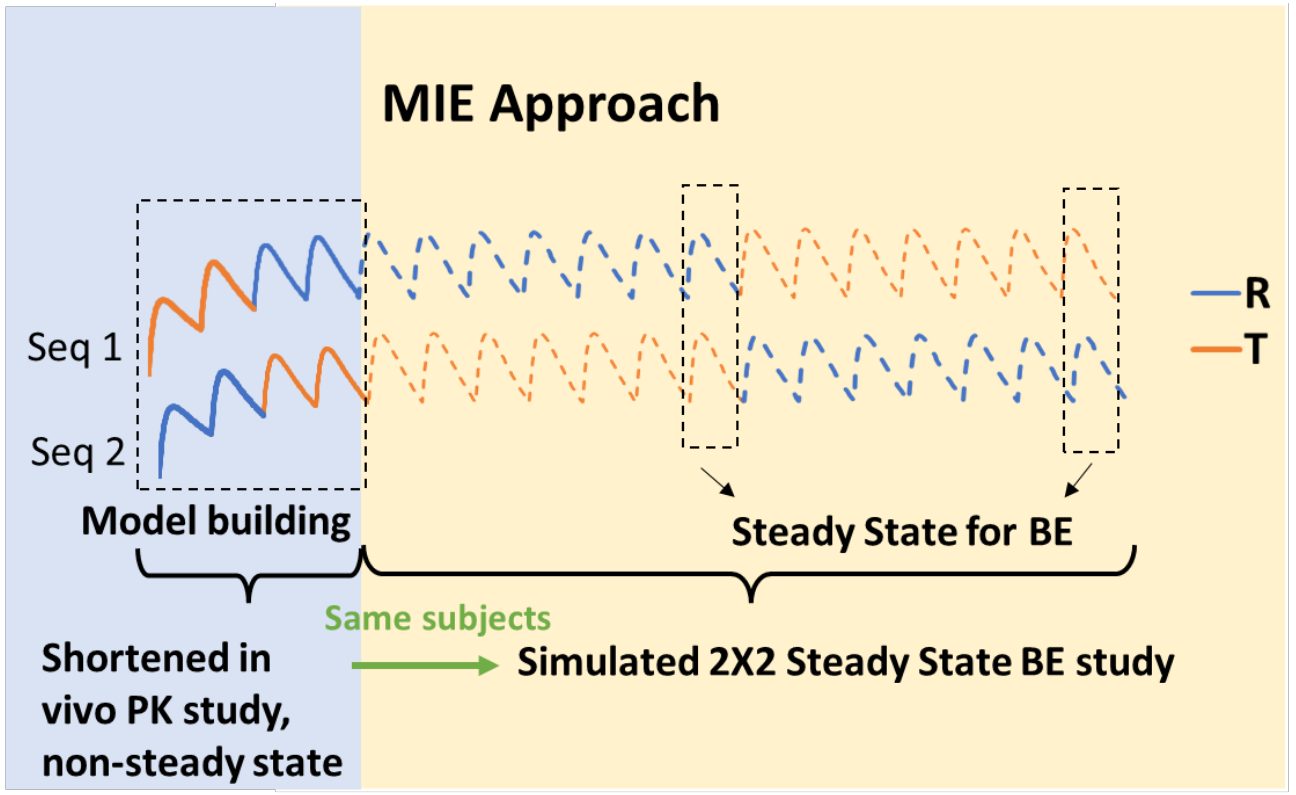
Steady state crossover BE study – long study duration

Opportunities for MIE in Generic LAI Development

- Generate pivotal evidence for BE decision
- Enhance the efficiency of BE studies
  - Alternative BE study
  - Shorter study duration
  - Smaller sample size
  - Alternative BE metrics associated with narrowed BE limits
- We see a clear demand: increased use of modeling approaches in Pre-ANDA meeting requests and ANDA submissions

Example 1 - Shorten BE Study: "In Silico" Dosing to Steady State

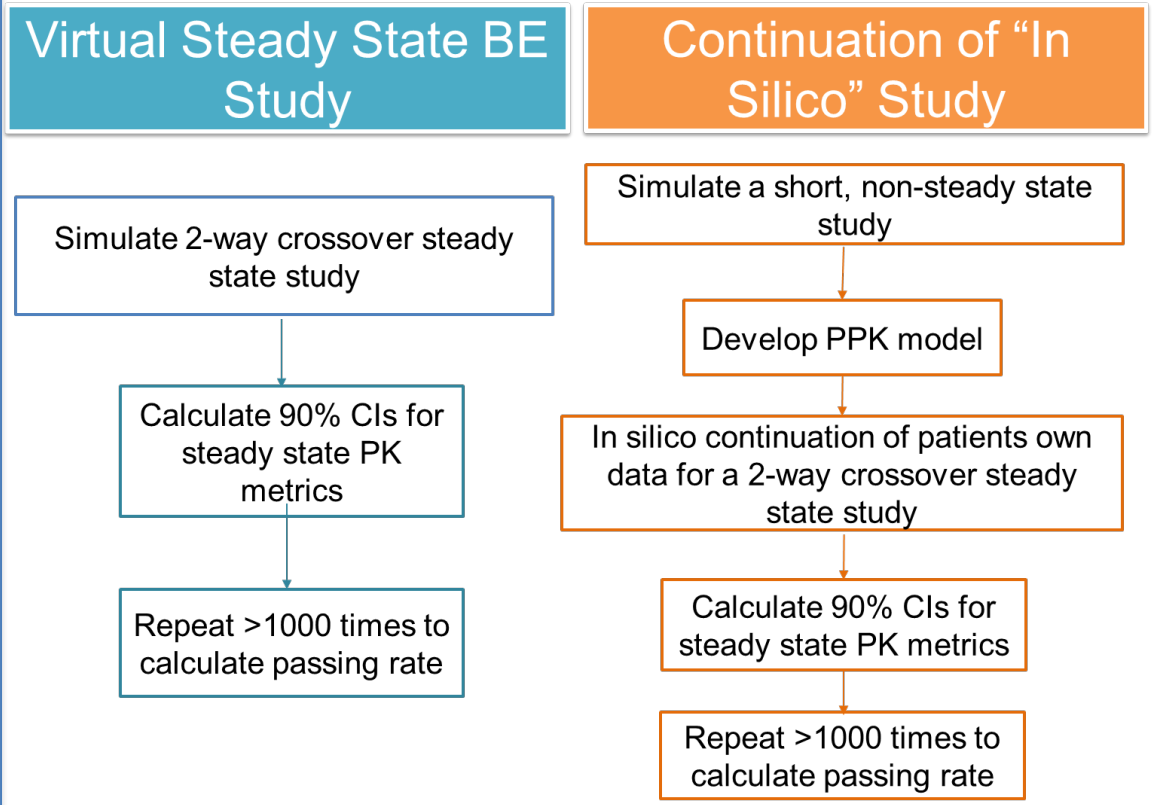




- Continuation of "in silico" dosing to the exact same group of individuals based on individual estimates
  - Actual clinical patient data will be collected
  - Clinical study will be adequately powered

Perform Clinical Trial Simulation To Select A Suitable Alternative Study Design

A Clinical Trial Simulation Process to Evaluate Power and Type-1 Error

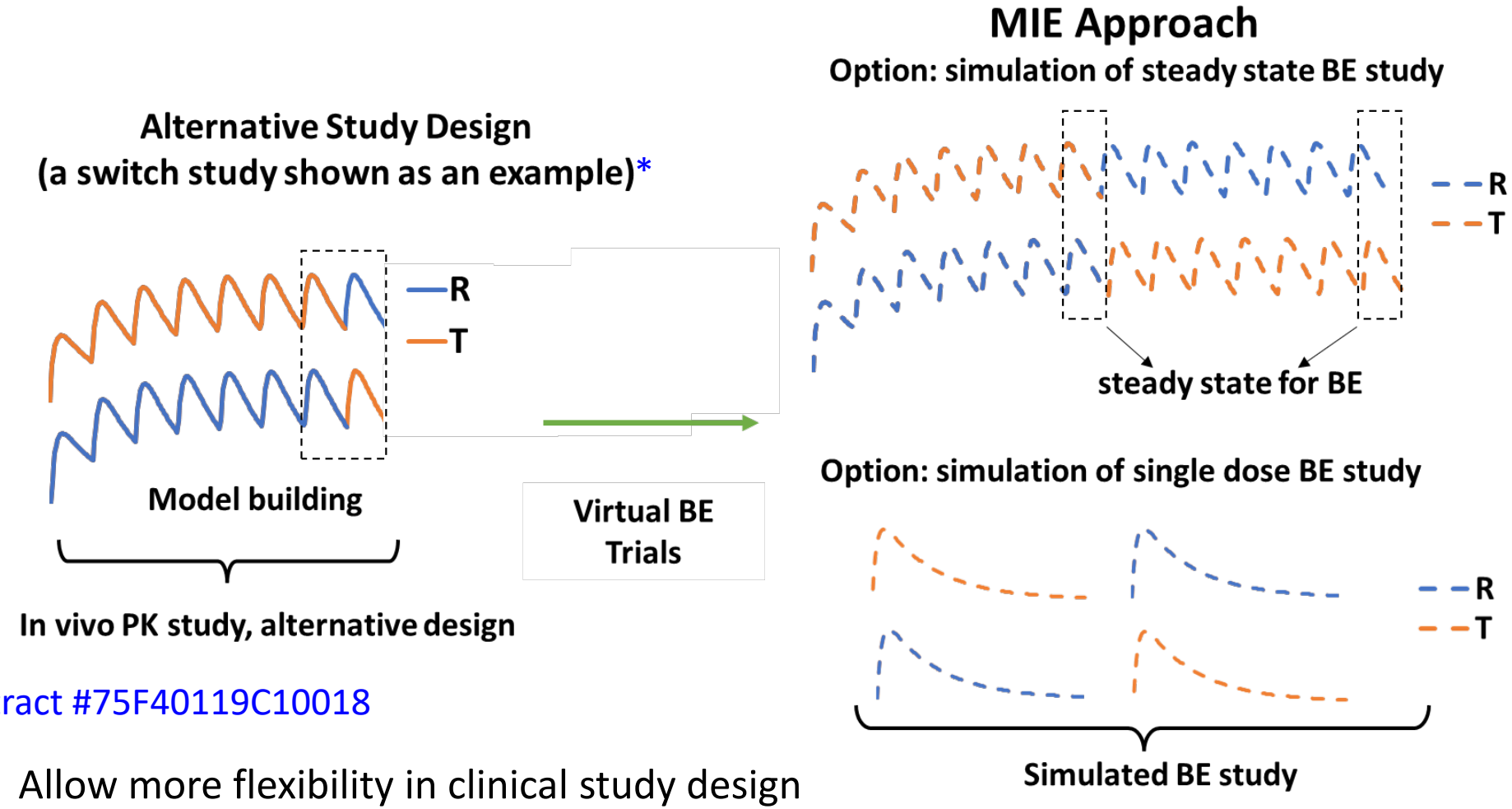


Power and Type-1 Comparisons for conventional and in silico continuation approach

Study Design	Design Description	In Vivo Study Duration	Study Power (%)	Type-1 Error (%)
A 2-way crossover SS study (N = X)	7 doses/trt period to SS	14 dosing intervals	>80	< 5
A shortened, non-SS, 2-way crossover study with "in silico" continuation to SS (N = X)	5 doses/trt period + simulation to SS	10 dosing intervals	> 80	< 5
	3 doses/trt period + simulation to SS	6 dosing intervals	> 80	< 5
	2 doses/trt period + simulation to SS	4 dosing intervals	> 80	< 5
	1 dose/trt period + simulation to SS	2 dosing intervals	< 80	> 5

Justifying the selection of a suitable in vivo study design based on good Power and Type-1 control in MIE BE.

Example 2 - Virtual BE Trials

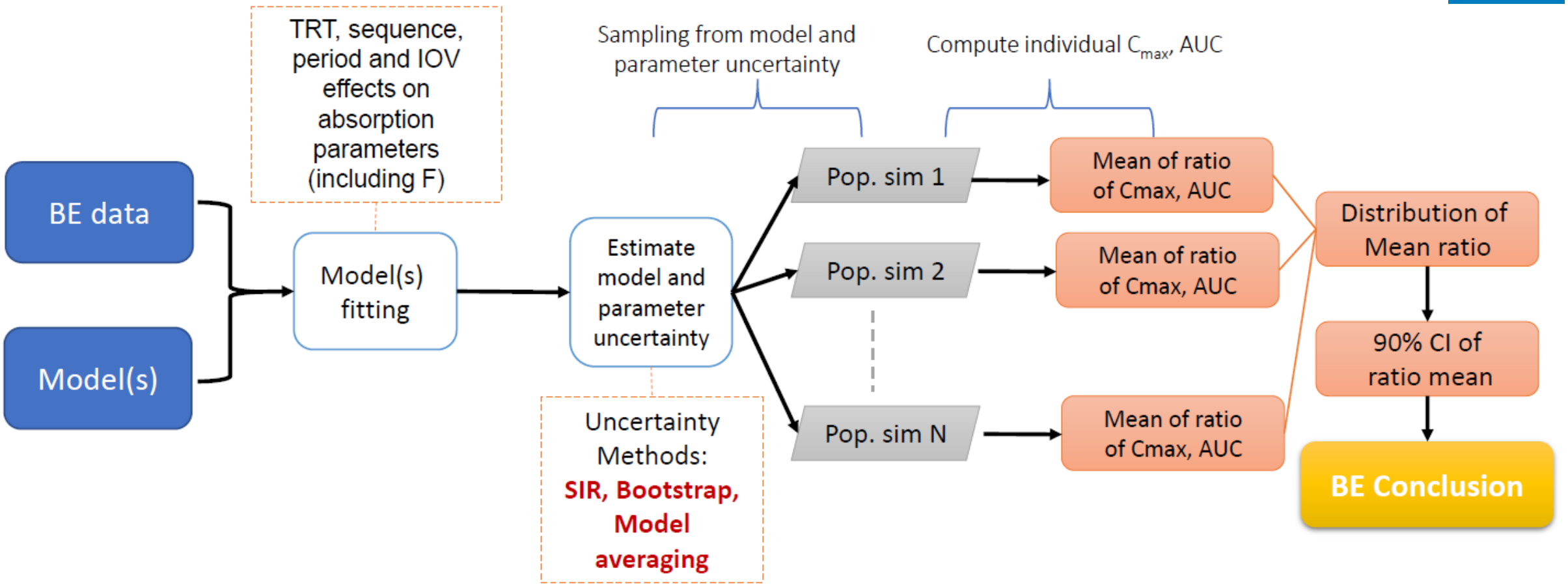


*FDA Research Contract #75F40119C10018

- Allow more flexibility in clinical study design
  - Simulate different virtual BE designs
  - Simulate additional subjects (model can be built on a small sample size to simulate results for a larger population)

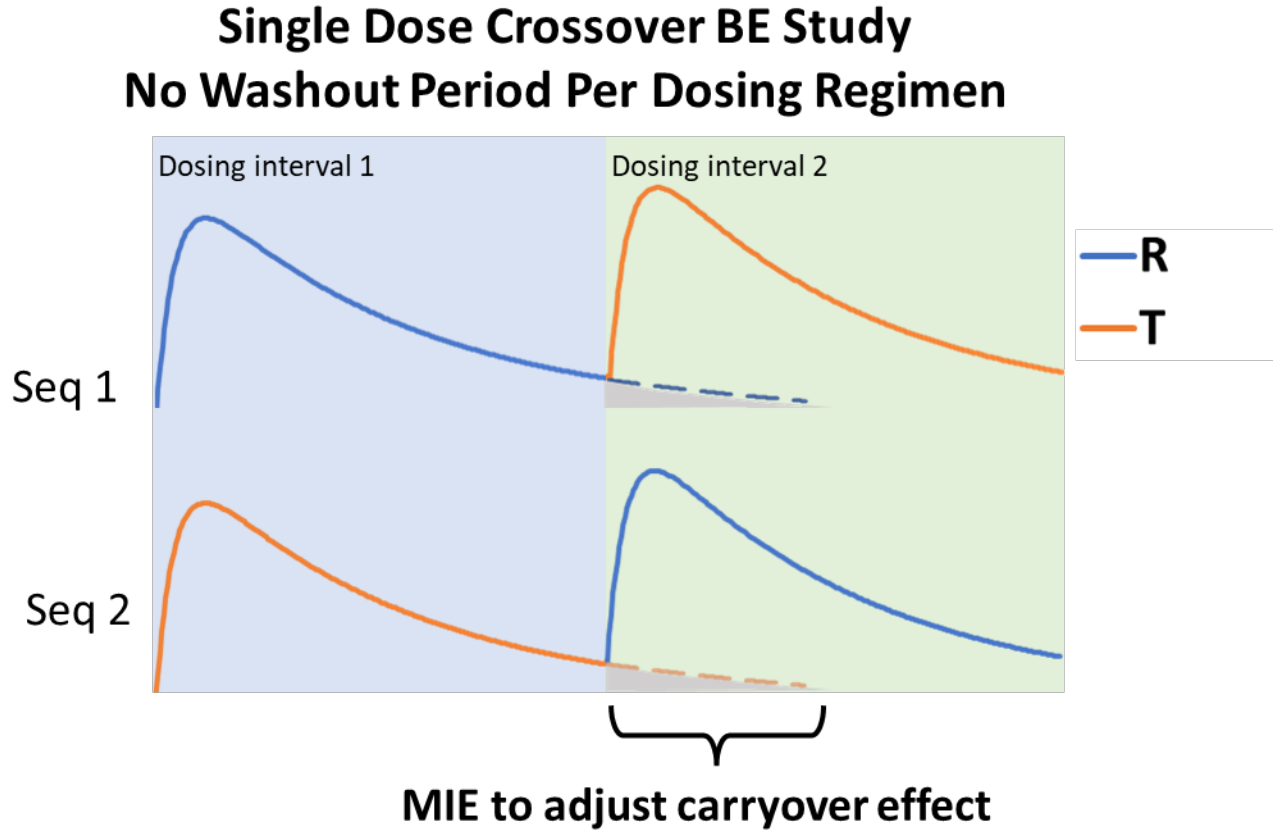
Example Virtual BE Framework

(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.

Example 3 - MIE to Adjust Carryover



- Adjusting carryover in a crossover study when the washout is not feasible – removing carryover via MIE
  - 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, Rockville, MD)*

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References

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- **FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Products:** https://www.fda.gov/drugs/generic-drugs/fda-ema-parallel-scientific-advice-pilot-program-complex-generichybrid-products
- **Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants:** https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/model-integrated-evidence-mie-industry-meeting-pilot-between-fda-and-generic-drug-applicants
- **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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