Generating Model-integrated Evidence for Developing and Approving Complex Generic LAI Products

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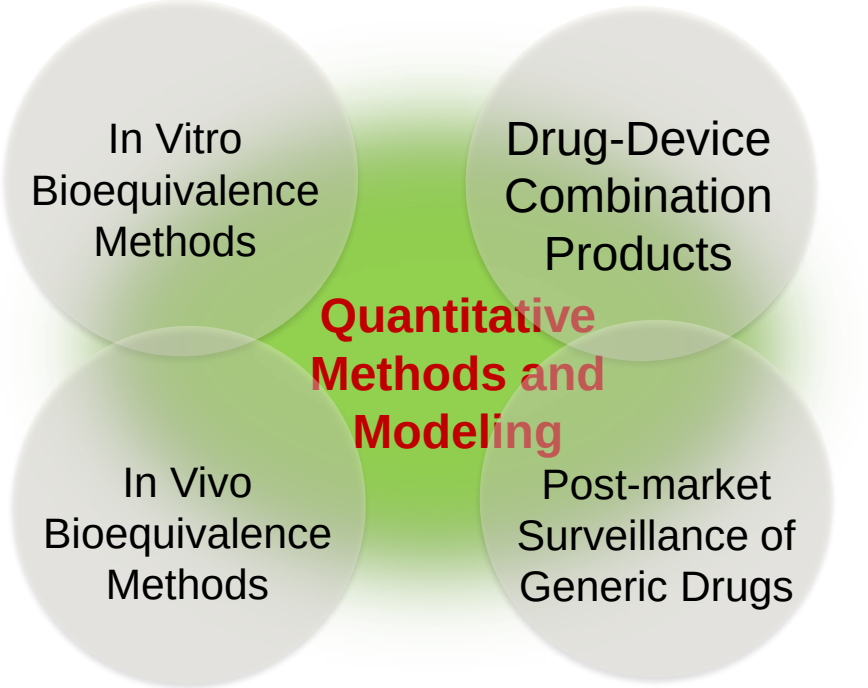
Disclaimer

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

The presenter is offering his perspective based upon his experiences during regulatory decision-making

Quantitative Methods & Modeling (QMM) for Generic Drug Development and Approval



Model-integrated evidence (MIE) refers to using model generated information such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence

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Long-Acting Injectable Drug Products

- Long-acting injectable (LAI) drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular, subcutaneous, intravitreal, or other routes.

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

Examples of FDA Approved Long-Acting Injectable Drug Products and Approved ANDAs

Trade Names	Ingredient	Indication	Dose Frequency	Approved Generic
ABILIFY MAINTENA KIT	ARIPIPRAZOLE	Schizophrenia; bipolar I disorder	Monthly	0
ARISTADA	ARIPIPRAZOLE LAUROXIL	Schizophrenia	Monthly, 6 weeks, 2 months	0
ARISTADA INITIO KIT	ARIPIPRAZOLE LAUROXIL	Schizophrenia	One time	0
SUBLOCADE	BUPRENORPHINE	Opioid use disorder	Monthly	0
PROBUPHINE	BUPRENORPHINE HYDROCHLORIDE	Opioid Dependence	one time (6 months)	0
CABENUVA KIT	CABOTEGRAVIR; RILPIVIRINE	HIV-1 treatment	Monthly	0
ATRIDOX	DOXYCYCLINE HYCLATE	Chronic adult periodontitis	1 week	0
BYDUREON BCISE	EXENATIDE	Improve glycemic control in type II diabetes	Weekly	0
BYDUREON...BYDUREON PEN	EXENATIDE SYNTHETIC	Improve glycemic control in type II diabetes	Weekly	0
YUTIQ	FLUOCINOLONE ACETONIDE	Chronic non-infectious uveitis affecting the posterior segment of the eye	36 months (one time)	0
ZOLADEX	GOSERELIN ACETATE	carcinoma of prostate, endometriosis, breast cancer	Monthly (4 weeks)	0
SUSTOL	GRANISETRON	Antiemetics for prevention of acute and delayed nausea and vomiting with chemotherapy	Weekly	0
LUPRON DEPOT...LUPRON DEPOT-PED	LEUPROLIDE ACETATE	Endometriosis, Fibroids, Advanced prostrate cancer; children with central precocious puberty	1,3,4,6 months	0
ELIGARD	LEUPROLIDE ACETATE	Palliative treatment of advanced prostate cancer	1,3,4,6 months	0
LUPANETA PACK	LEUPROLIDE ACETATE; NORETHINDRONE ACETATE	Endometriosis	Monthly	0
DEPO-PROVERA	MEDROXYPROGESTERONE ACETATE	Prevention of Pregnancy	3 months	1
DEPO-SUBQ PROVERA 104	MEDROXYPROGESTERONE ACETATE	Prevention of pregnancy, endometriosis-associated pain	3 months	0
SINUVA	MOMETASONE FUROATE	Nasal polyps who had ethmoid surgery	3 months (one time)	0
VIVITROL	NALTREXONE	Alcohol/Opioid Dependence	Monthly (4 weeks)	0
SANDOSTATIN LAR	OCTREOTIDE ACETATE	Acromegaly, Carcinoid Tumors and Vasoactive Intestinal Peptide secreting tumors	Monthly (4 weeks)	0
ZYPREXA RELPREVV	OLANZAPINE PAMOATE	Schizophrenia	2, 4 weeks	0
INVEGA SUSTENNA	PALIPERIDONE PALMITATE	Schizophrenia, schizoaffective disorder, mood stabilizers or antidepressants	Monthly	0
INVEGA TRINZA	PALIPERIDONE PALMITATE	Schizophrenia	3 months	0
SIGNIFOR LAR KIT	PASIREOTIDE PAMOATE	Acromegaly, Cushing's Disease	4 weeks	0
PERSERIS KIT	RISPERIDONE	Schizophrenia	Monthly	0
RISPERDAL CONSTA	RISPERIDONE	Schizophrenia, Bipolar I Disorder	2 weeks	0
XYOSTED (AUTOINJECTOR)	TESTOSTERONE ENANTHATE	Testosterone replacement therapy	weekly	0
ZILRETTA	TRIAMCINOLONE ACETONIDE	Osteoarthritis pain of the knee	3 months (one time)	0
TRIPTODUR KIT	TRIPTORELIN PAMOATE	precocious puberty	24 weeks	0
TRELSTAR	TRIPTORELIN PAMOATE	Advanced prostrate cancer	4/12/24 weeks	0

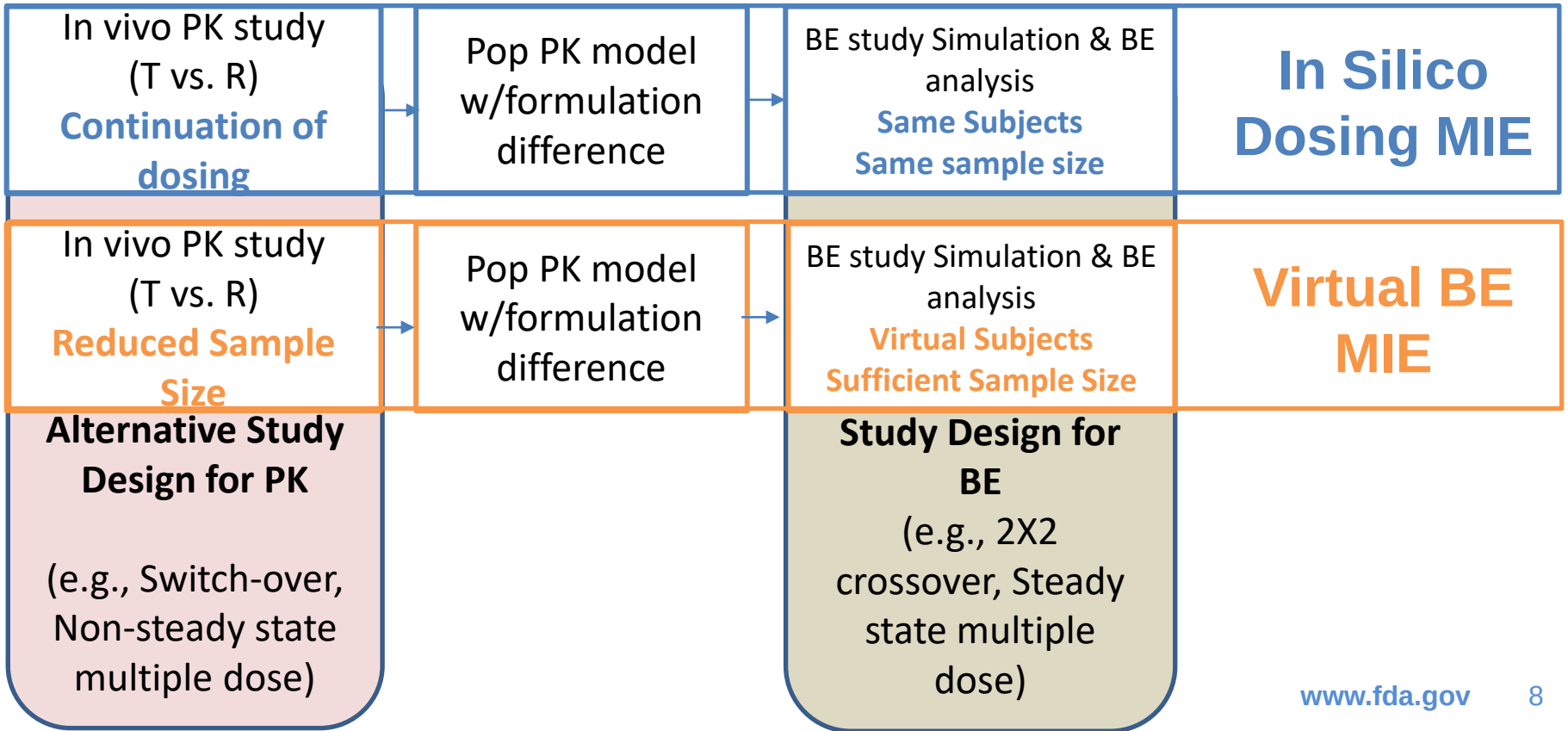
Challenges in LAI Product Development and Lifecycle Management

- Long apparent half-life:
  - Longer time to reach steady state
  - Longer wash out time
  - Longer duration for bioequivalence (BE) studies
  - High drop out rate
  - Not practical to perform a single-dose crossover BE study
- Challenging to propose relevant dosing scenarios, e.g.,
  - Impact of early, delayed or missed doses
  - Switching between formulations

Opportunities for Modeling and Simulation in LAI Product Development

- Dosing regimen
  - Justification for dosing recommendation for missed doses
  - Impact of early, delayed, or missed doses
  - Dose adjustment for special population
- Bridging results from previous studies/application
- Reducing cost, time; increasing efficiency

Two Major Types of Population PK-MIE for BE



Recent Examples of Population PK-MIE In Silico Dosing

- Proposals for some LAIs, oncology, orphan drugs in pre-ANDA meetings
- **Shorter duration** in vivo PK studies (LAI)
- Reduced sample size and treatment cycle-compatible in vivo PK studies (oncology/orphan drugs)

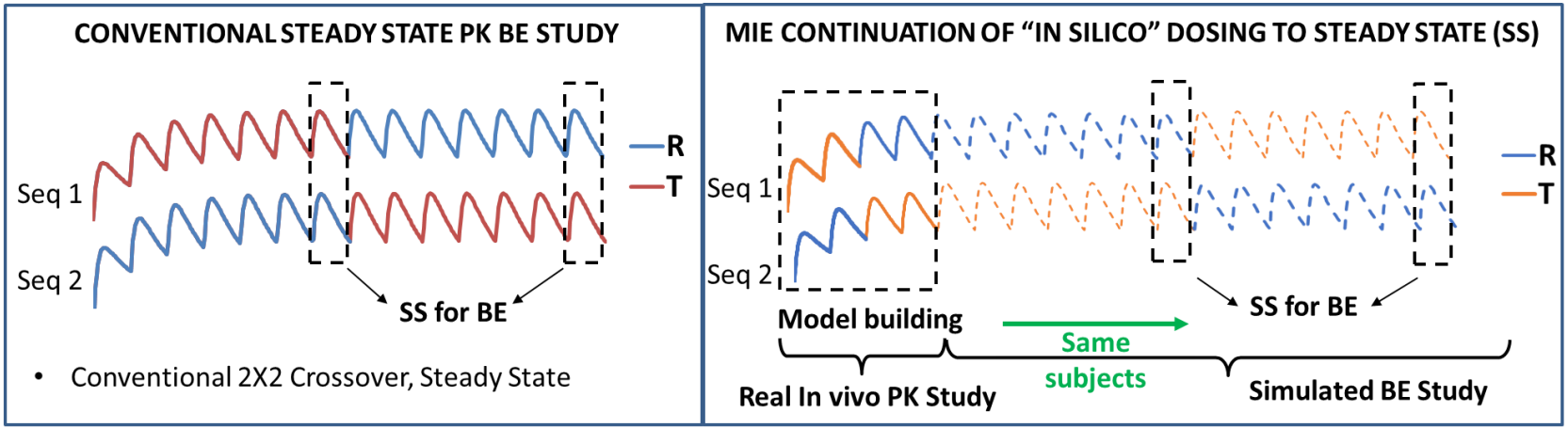
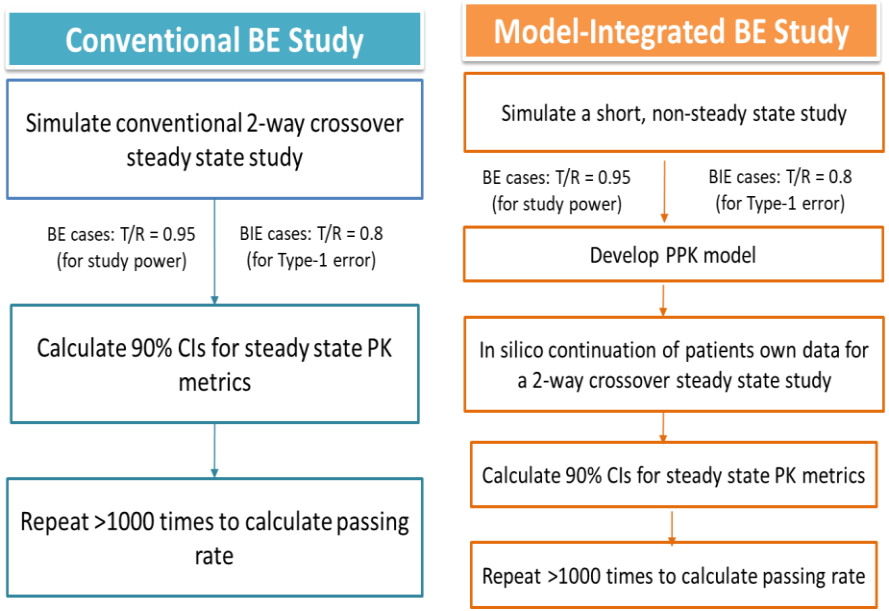


Illustration of In silico Dosing MIE for LAI products

A Case Example of In Silico Dosing MIE for a LAI

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



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

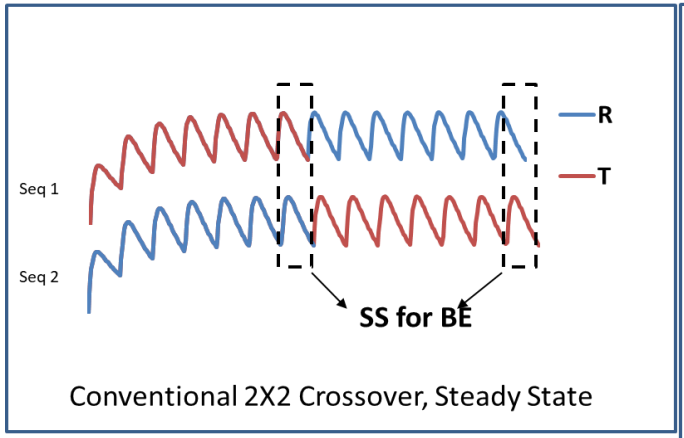
Study Design	Design Description	In Vivo Study Duration	Study Power (%)	Type-1 Error (%)
Conventional, 2-way crossover study (N=40)	7 month/trt period	14 months	> 80	< 5
Shortened 2-way crossover study with "in silico" continuation (N=40)	5 month/trt period + simulation to SS	10 months	> 80	< 5
	3 month/trt period + simulation to SS	6 months	> 80	< 5
	2 month/trt period + simulation to SS	4 months	> 80	< 5
	1 month/trt period + simulation to SS	1 months	< 80	> 5

Preliminary results suggest that a suitable model-based design would require at least 2 doses for each treatment, yielding a total duration of 4 months, with good Power and Type-1 control.

Slide provided by Courtesy of Dr. Yuqing Gong

Recent Examples of Population PK-MIE Virtual BE

- Proposals for some oncology/orphan drugs in pre-ANDA meetings
- **Reduced sample size** and shorter duration in vivo PK studies
- MIE framework for LAIs by Uppsala University (GDUFA research)



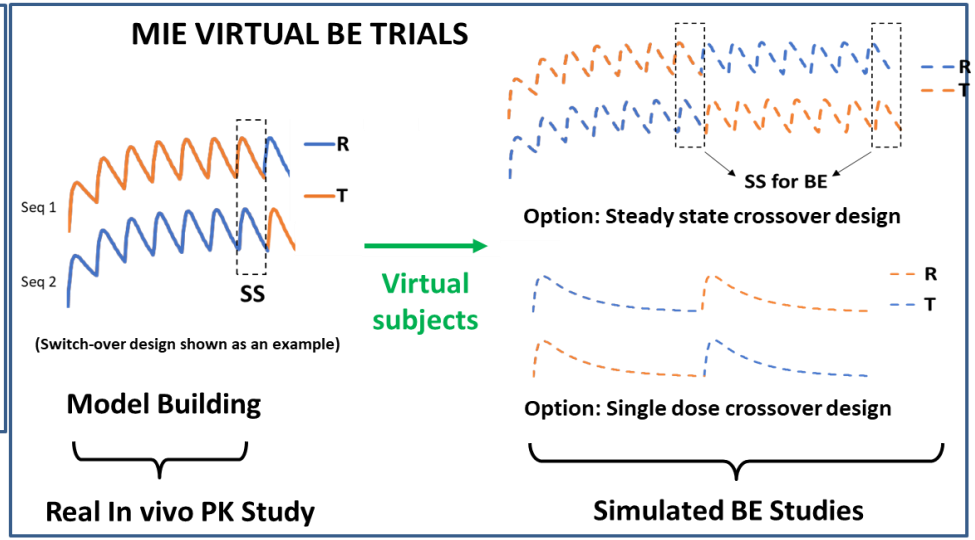
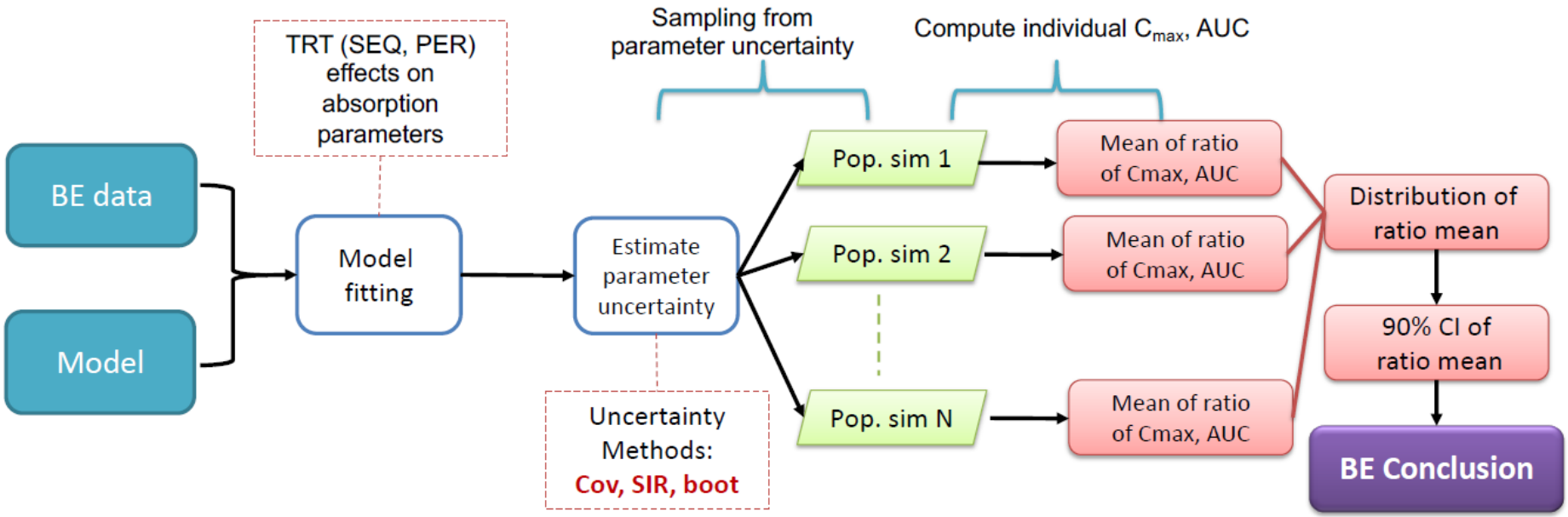


Illustration of Virtual BE MIE for LAI products

Model Building and Validation and VBE Simulation Process



Slide adapted from ACOP presentation by Andrew Hooker 2019

Common Deficiencies in MIE VBE

- The applicant did not submit a modeling analysis plan (MAP)
- The applicant did not evaluate the type I error before virtual BE simulation
- The model is not able to detect potential formulation difference between test and reference product
- The sample size of virtual BE simulation is a lot larger than the sample size of clinical BE study for model building without sufficient justifications
- The applicant did not understand that the model building and validation in BE decision is more stringent than the pop-PK modeling in new drug development.

Key Considerations for Applying MIE to Regulatory BE Decision

Pop-PK guidance

Variability
- Between-Subject
- Within-Subject (e.g., occasion, period)
- Residual error (e.g., measurement)
- Covariates

Numerical
- Convergence
- Parameter SE (%)
- Shrinkage (%) etc.

Graphical diagnostic
- Obs vs. IPRED
- CWRES vs. Time
- VPC for T&R, PER, etc.

Detect formulation difference
- TRT (SEQ, PER) effects on absorption parameters

PK metrics
- Cmax, AUCt, AUCinf
- Obs. within simulated [5%, 95%] for T&R, Per, etc.

Type I Error
Sensitive to detect formulation difference
- Identify parameters for T/R ratio of all PK metrics
- T/R ratio at boundary of 80% and 125%

Type II Error
Applicant's responsibility
Power and sample size
- e.g., T/R ratio at 95%, 100%, 111.11% etc.

Sampling
- Parameter uncertainty

PK metrics
- All PK metrics
- NCA method
- Simulated method

Possible approaches
- Model-based BE
- Conventional Model Averaging
- Bootstrap Model Selection
- Model-informed (Switch study, covariates effect)

Data sources
- Clinical studies + Data imputation Simulation

Model uncertainty
- Sufficient replicate simulations

PK metrics
- 90% CI of T/R ratio for all PK metrics should fall within [80%, 125%].

Modeling Uncertainty Estimation | **Model Validation** | **Type I and Type II Error** | **Simulation** | **BE Conclusion**

Adapted from the SBIA presentation in September 2022, Courtesy of Dr. Kairui (Kevin Feng)

Future Perspectives

- Further cost saving via
  - Reduction in clinical study size and duration
  - Optimization of study design
- Improving simulation technique
  - Model averaging
  - Non model averaging
  - Bayesian method (Markov Chain Monte Carlo)?
- Model validation
  - Population PK guidance
  - Additional considerations for MIE BE
- Model sharing, submission, communication
  - Modeling Analysis Plan
  - Model Master Files