Application of quantitative modeling and simulations to bioequivalence determination for Long-Acting Injectables – sharing research progress and regulatory experience

Small Business & Industry Assistance (SBIA)

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Kairui (Kevin) Feng, Ph.D.
Staff Fellow
Quantitative Clinical Pharmacology Team
Division of Quantitative Methods and Modeling
Office of Research and Standards
Office of Generic Drugs| CDER | U.S. FDA

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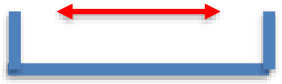
Outline

- Understand challenges in pharmacokinetic (PK) bioequivalence (BE) studies for long-acting injectable (LAI) drugs
- Opportunities with model-integrated BE approach
  - GDUFA Research program
- Collaboratively advancing the field with industry and other stakeholders
  - FDA's regulatory experience in Pre-ANDA meetings
- Conclusion
- Discussion for future directions

Challenges in BE Studies for LAIs

- Long half-life due to slow release of drug from formulation, not elimination
- Challenges in patient recruitment
- High Drop-outs
- Attainment of steady state for LAIs

A few days to a few weeks



Common BE study duration
Healthy subjects
Single dose

A few months to a few years

LAI BE study duration
Patient
Steady state

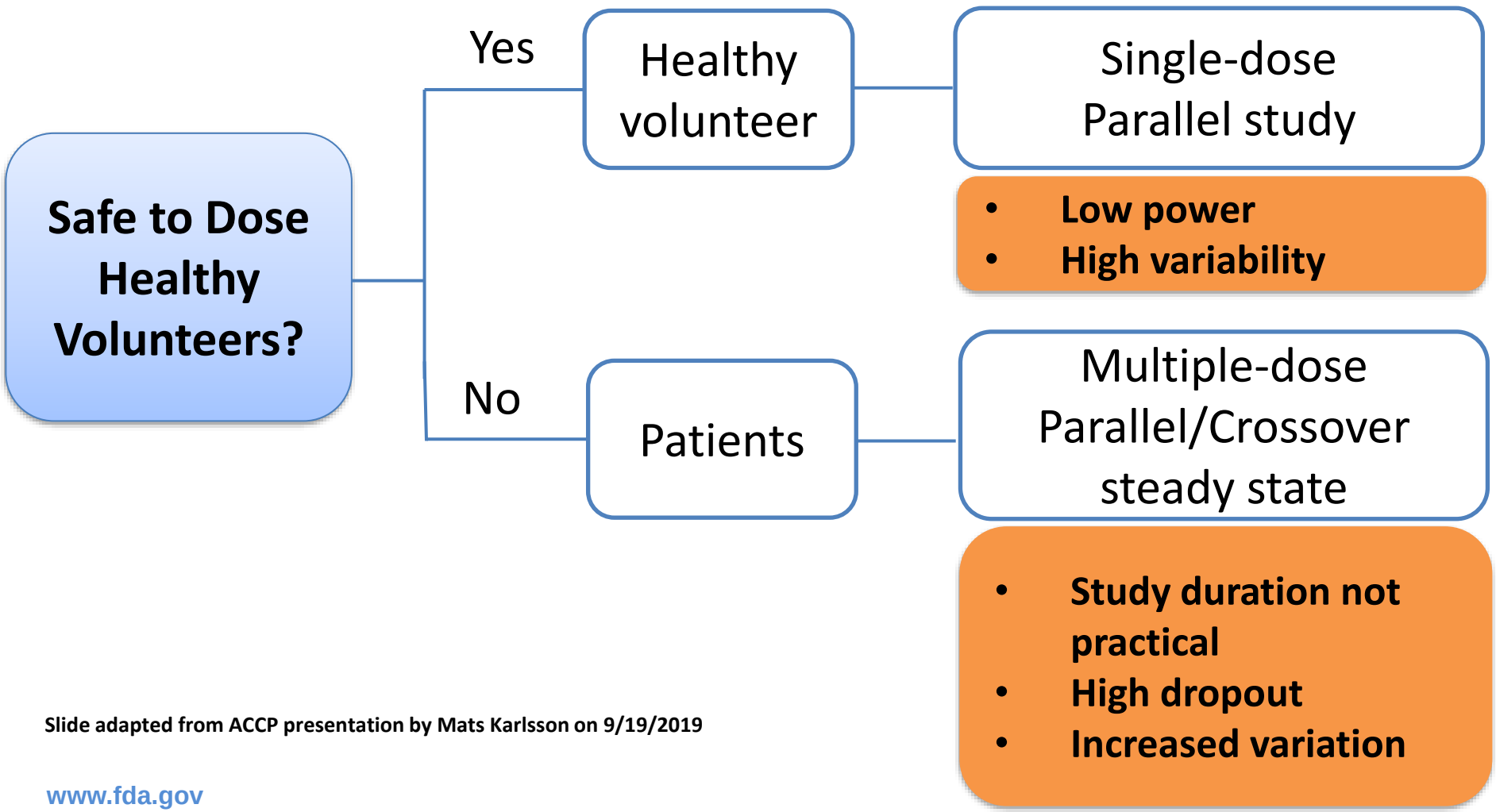
Other challenges for controlled release over an extended duration

Matthew N O'Brien, Wenlei Jiang, Yan Wang, David M. Challenges and opportunities in the development of complex generic long-acting injectable drug products, 2021 Aug 10;336:144-158. doi: 10.1016/j.jconrel.2021.06.017. https://pubmed.ncbi.nlm.nih.gov/34126170/

Examples of FDA Approved LAI Drug Products and Approved ANDAs

Trade Names	Ingredient	Indication	Dose Frequency	Approved Generic
ABILIFY MAINTENA KIT	ARIPIPRAZOLE	Schizophrenia; bipolar I disorder	Monthly	No
ARISTADA	ARIPIPRAZOLE LAUROXIL	Schizophrenia	Monthly, 6 weeks, 2 months	No
ARISTADA INITIO KIT	ARIPIPRAZOLE LAUROXIL	Schizophrenia	One time	No
SUBLOCADE	BUPRENORPHINE	Opioid use disorder	Monthly	No
PROBUPHINE	BUPRENORPHINE HYDROCHLORIDE	Opioid Dependence	one time (6 months)	No
ATRIDOX	DOXYCYCLINE HYCLATE	Chronic adult periodontitis	1 week	No
BYDUREON BCISE	EXENATIDE	Improve glycemic control in type II diabetes	Weekly	No
BYDUREON...BYDUREON PEN	EXENATIDE SYNTHETIC	Improve glycemic control in type II diabetes	Weekly	No
YUTIQ	FLUOCINOLONE ACETONIDE	Chronic non-infectious uveitis affecting the posterior segment of the eye	36 months (one time)	No
ZOLADEX	GOSERELIN ACETATE	carcinoma of prostate, endometriosis, breast cancer	Monthly (4 weeks)	No
SUSTOL	GRANISETRON	Antiemetics for prevention of acute and delayed nausea and vomiting with chemotherapy	Weekly	No
LUPRON DEPOT...LUPRON DEPOT-PED	LEUPROLIDE ACETATE	Endometriosis, Fibroids, Advanced prostrate cancer; children with central precocious puberty	1,3,4,6 months	No
ELIGARD	LEUPROLIDE ACETATE	Palliative treatment of advanced prostate cancer	1,3,4,6 months	No
LUPANETA PACK	LEUPROLIDE ACETATE; NORETHINDRONE ACETATE	Endometriosis	Monthly	No
DEPO-PROVERA	MEDROXYPROGESTERONE ACETATE	Prevention of Pregnancy	3 months	Yes
DEPO-SUBQ PROVERA 104	MEDROXYPROGESTERONE ACETATE	Prevention of pregnancy, endometriosis-associated pain	3 months	No
SINUVA	MOMETASONE FUROATE	Nasal polyps who had ethmoid surgery	3 months (one time)	No
VIVITROL	NALTREXONE	Alcohol/Opioid Dependence	Monthly (4 weeks)	No
SANDOSTATIN LAR	OCTREOTIDE ACETATE	Acromegaly, Carcinoid Tumors and Vasoactive Intestinal Peptide secreting tumors	Monthly (4 weeks)	No
ZYPREXA RELPREVV	OLANZAPINE PAMOATE	Schizophrenia	2, 4 weeks	No
INVEGA SUSTENNA	PALIPERIDONE PALMITATE	Schizophrenia, schizoaffective disorder, mood stabilizers or antidepressants	Monthly	Yes
INVEGA TRINZA	PALIPERIDONE PALMITATE	Schizophrenia	3 months	No
SIGNIFOR LAR KIT	PASIREOTIDE PAMOATE	Acromegaly, Cushing's Disease	4 weeks	No
PERSERIS KIT	RISPERIDONE	Schizophrenia	Monthly	No
RISPERDAL CONSTA	RISPERIDONE	Schizophrenia, Bipolar I Disorder	2 weeks	No
XYOSTED (AUTOINJECTOR)	TESTOSTERONE ENANTHATE	Testosterone replacement therapy	weekly	No
ZILRETTA	TRIAMCINOLONE ACETONIDE	Osteoarthritis pain of the knee	3 months (one time)	No
TRIPTODUR KIT	TRIPTORELIN PAMOATE	precocious puberty	24 weeks	No
TRELSTAR	TRIPTORELIN PAMOATE	Advanced prostrate cancer	4/12/24 weeks	No

Challenges Associated with Different Types of LAI BE Studies



- **Contraceptive**
  - Medroxyprogesterone acetate
- **To treat alcohol/drug dependence**
  - Naltrexone

- **Antipsychotic**
  - Paliperidone palmitate
  - Aripiprazole
  - Risperidone
  - Olanzapine pamoate

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

Opportunities with Modeling

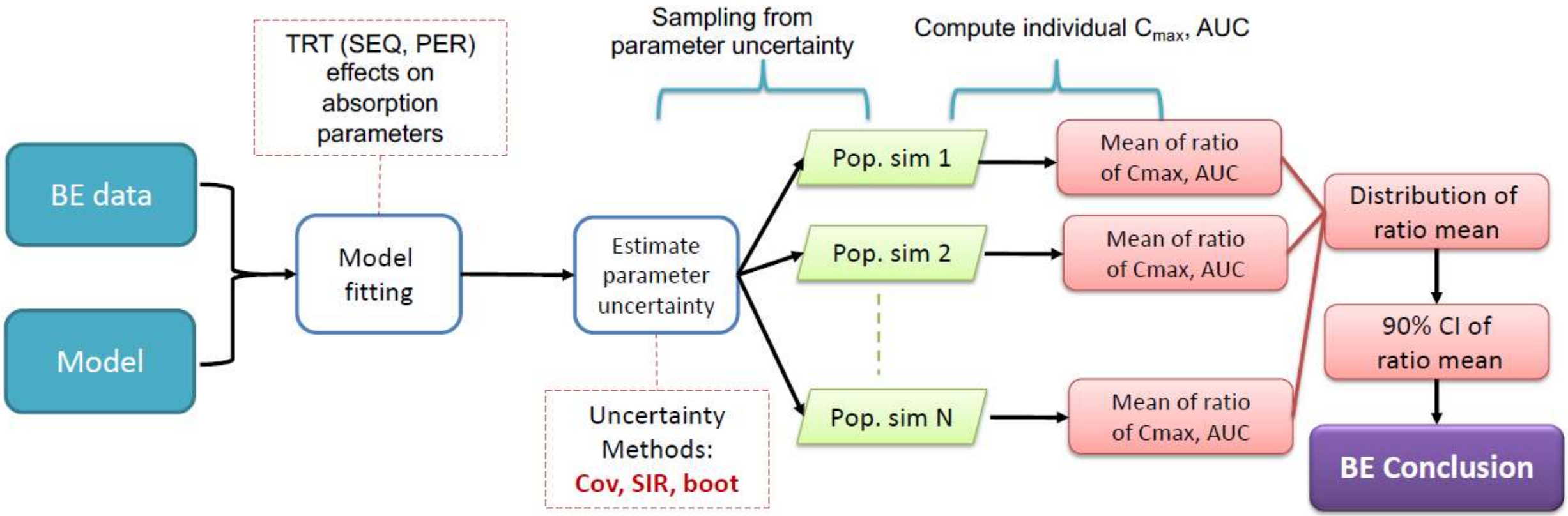
- Address some of the main issues in *in vivo* BE studies
  - shorter treatment duration
  - smaller sample size
- Industry shared challenges/requests at FY 2022 Generic Drug Science and Research Initiatives Workshop
  - Modeling and analysis proposals included in Pre-ANDA submissions often result in Information Requests.
  - Specific expectations for model integrated evidence are lacking.
  - Provide clarity on extent of validation/validation criteria necessary for models to replace in vivo BE studies (e.g., population PK models, PBPK models).
  - Development of in vitro biorelevant/biopredictive methodologies for complex products (e.g., inhalation, LAI, ophthalmic) to be used to provide model input.
  - Align with other Regulatory Agencies (i.e., EMA) on acceptance of MIDD.
  - Single-dose BE study in healthy subjects instead of multiple dose BE study in patients.

EMA – European Medicines Agency; MIDD – model informed drug development

Research Progress: FDA-Funded Grants/Contracts Modeling and Simulation for LAI Products

Project title	Study duration	Grantee/Contractor	Grant/Contract No.
Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	2015-2019	University of Utah	U01FD005442
Development of PBPK simulation for long-acting injectable microspheres	2015-2018	Simulations Plus Inc.	U01FD005463
Development of model-informed bioequivalence evaluation strategies for long-acting injectable products	**2019-2021**	**Uppsala University**	**75F40119C10018**
Enhancement and validation of in vitro – in vivo correlation method for long-acting injectable drug products to accelerate their generic development	2021-2024	University of Connecticut	75F40121C00133

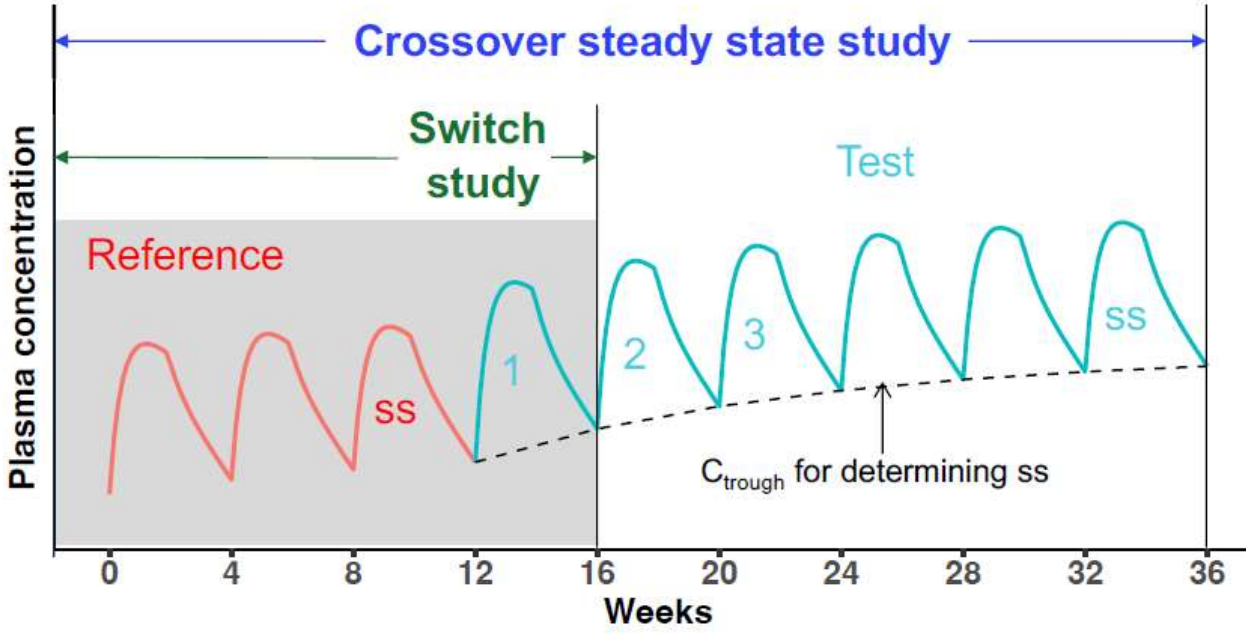
GDUFA Research Developed Model-integrated BE Approaches



Slide adapted from ACOP presentation by Andrew Hooker 2019

Model-Integrated Evidence (MIE) Opportunity 1: Possible solution to reduce BE study duration

Example – innovative study design that uses switch study instead of crossover SS



Model-informed BE method

BE data

↓

PK metrics from NCA

↓

Standard method: LMEM

$$\log(AUC_{ij}) = AUC_{ref} + \beta_{AUC} \times TRT_{ij} + \eta_{AUC,i} + \varepsilon_{AUC,ij}$$
$$\log(Cmax_{ij}) = Cmax_{ref} + \beta_{Cmax} \times TRT_{ij} + \eta_{Cmax,i} + \varepsilon_{Cmax,ij}$$

↓

90% confidence interval of β_{AUC}
90% confidence interval of β_{Cmax}

↓

BE conclusion based on adjusted BE criteria

Case-specific Example:

AUC(%) : (94.15, 107.04)
Cmax (%): (95.59, 107.25)

Slide adapted from ACOP presentation by Andrew Hooker 2019

*** NCA – Noncompartmental Analysis, LMEM – linear mixed effects model**

MIE Opportunity Example 2: Covariate Effects in Statistical Model for Parallel Study

Covariates identified from population-PK model

Model-informed BE method

Increase in Power

BE data

↓

PK metrics from NCA

↓

Method: LMEM

$$\log(AUCinf_i) = AUCinf_{ref} + 0.0022\times AGE_i - 0.0053\times AGE_i + \beta_{AUCinf}\times TRT_i + \varepsilon_{AUCinf,i}$$

$$\log(AUClast_i) = AUClast_{ref} + 0.0042\times AGE_i - 0.087\times SEX_i - 0.0053\times CLCR_i + 0.0576\times INJS_i + \beta_{AUClast}\times TRT_i + \varepsilon_{AUClast,i}$$

$$\log(Cmax_i) = Cmax_{ref} + 0.0055\times AGE_i - 0.0049\times CLCR_i - 0.0255\times BMI_i - 0.2171\times SEX_i + 0.2887\times INJS_i + \beta_{Cmax}\times TRT_i + \varepsilon_{Cmax,i}$$

↓

90% confidence interval of β_{AUC}

90% confidence interval of β_{Cmax}

↓

BE conclusion based on adjusted BE criteria (80%, 125%)

Overview of Regulatory Experience at FDA

- Applicant proposed a M&S approach for BE decision by recruiting smaller sample size in pivotal study.
  - Acceptable. Detailed modeling analysis plan (MAP) should be submitted for assessment.
- Applicant proposed a population PK (PPK) model which was developed from literatures. Simulations were performed to assess the potential impact of missing PK samples (due to COVID-19 interruption) on type 1 error.
  - Not acceptable. The PPK models should be developed using actual clinical data, be fully validated, be capable to detect the formulation difference and be used for imputation to investigate the impacts on missing PK samples.
  - Acceptable. After revising the modeling strategy, applicant provided sufficient justifications for assessment.

Overview of Regulatory Experience at FDA - Continued

- Applicant submitted a population PK model using modeling and simulation approach and provided a modeling analysis plan.
  - Reasonable. However, further justifications need to be provided.
- Applicant proposed a mechanistic erosion-based PBPK model which incorporates in vitro and in vivo data with the associated scientific literature for a virtual BE simulation.
  - Insufficient. Mechanistic PBPK model should be able to detect potential formulation difference with proper estimation for type I and type II errors. Comments on details of the modeling strategy were provided.

MIE is rapidly evolving
Common deficiencies

- The applicant did not submit a modeling analysis plan (MAP).
- Type I error results were based on literature model.
- The applicant did not evaluate the type I error before virtual BE simulation.
- The overall modeling approach is lack of supporting materials for modeling process.
- The model (pop-PK or PBPK) 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 Components of M&S FDA considers for MIE

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**

Challenge Questions #1

- **Which of the following statements is true?**

A. Applicant can propose a model integrated evidence as an alternative BE approach without detailed model building and validation process plan.

B. The model should be able to detect the sensitivity of formulation difference and provide confidence in simulation for BE decision.

C. Applicant can use a smaller sample size in pivotal study and use M&S for virtual BE simulation without considering uncertainty.

Challenge Questions #2

- **Which of the following statements is NOT true?**

A. Due to the COVID-19 situation, modeling and simulation approach can be used for BE decision by recruiting smaller sample size in pivotal study, providing with detailed modeling analysis plan.

B. Due to the COVID-19 public health emergency, a large number of PK samples were missing. A population PK (PPK) model can be developed using actual clinical data, be fully validated, be capable to detect the formulation difference, and be used for imputation to investigate the impacts on missing PK sample.

C. Applicant can propose a mechanistic erosion-based PBPK model which incorporates in vitro and in vivo data with the associated scientific literature for a virtual BE simulation without providing the sensitivity of detecting formulation difference.

Conclusions

- A few possible MIE approaches using M&S for LAI BE assessment were proposed by recent FDA Funded Grants/Contracts from research institutes, including:
  - Model simulation to conclude BE
    - Model-integrated BE
    - Conventional Model Averaging
    - Bootstrap Model Selection
  - Model to inform BE statistical model
    - Switch study for adjustment of BE limits
    - covariates effect
- FDA is committed to advancing this area and has been providing guidance to industry via pre-ANDA meetings and incorporating the feedback from key stakeholders via public workshops.
- FDA encourages innovative M&S approaches to overcome the challenges of BE assessment, but detailed modeling analysis plan (MAP) should be submitted for evaluation.

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