Leveraging Modeling and Simulation to Make Regulatory Impacts for Long-Acting Generic Drug Approvals

CRS Pre-Meeting Workshop:
Equivalence of Complex Long Acting Drugs Workshop
July 2nd, 2020
Session IV: Modeling and Simulation Strategies

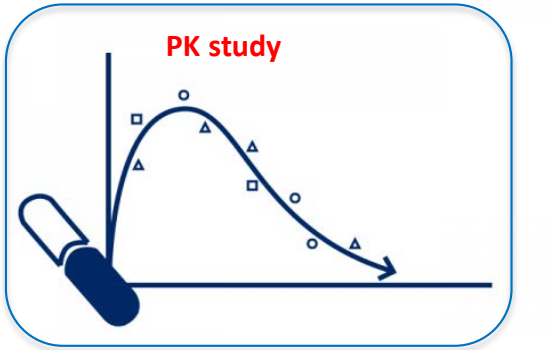
Liang Zhao, PhD
Division of Quantitative Methods & Modeling
Office of Research and Standards, Office of Generic Drugs, CDER, FDA

Disclaimer

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

Application of Pharmacokinetic Studies in NDA and ANDA Drug Development Process

Pharmacokinetic (PK) studies assess bioavailability (BA) and bioequivalence (BE) in New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA)



New Drug Application (NDA)

- *Establish **safety and efficacy** of the investigational new drug by phase-I, phase-II and Phase-III clinical trials.*
  - *Phase-I : Safety, tolerability, PK, biomarkers, proof of principle*
  - *Phase-II: Efficacy, guidance of dose and dosing regimen*
  - *Phase-III : confirmation of efficacious dose, benefit/risk ratio, sub-group selection*

Abbreviated NDA (ANDA)

- *Establish **BE** of the generic drug product to that of the reference listed drug (RLD) by pharmacokinetic measure of –*
  - *Rate of absorption (peak exposure)*
  - *Extend of absorption (total exposure)*
  - *Partial exposure*

Long-Acting Injectable Drug Products

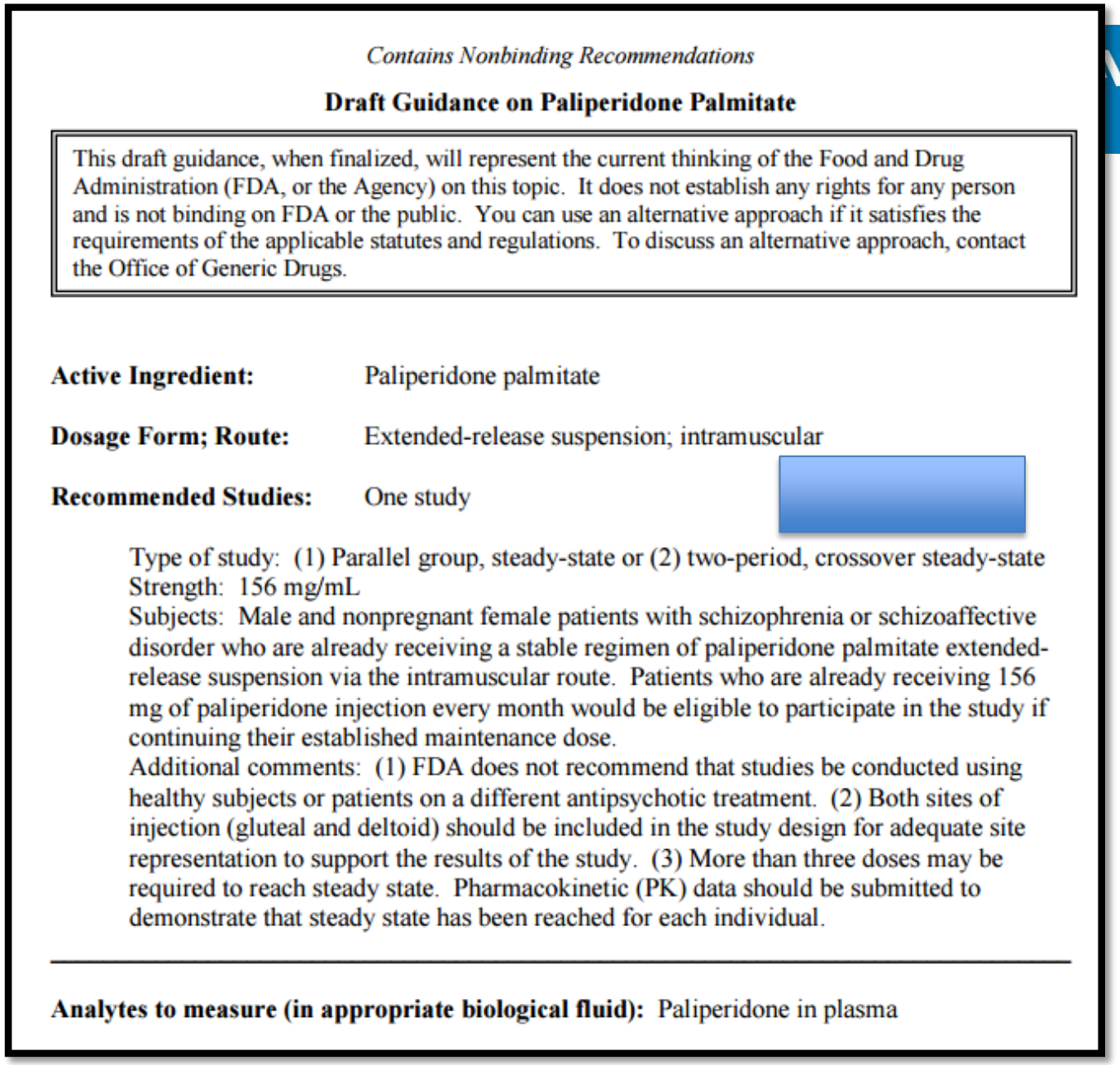
- Long-acting injectable (LAI) drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular, subcutaneous, intravitreal, or other routes.
- These products can help improve patient compliance with a better therapeutic option to treat patients who may adhere poorly to frequent injectable medications.

Examples of FDA Approved Long-Acting Injectable Drug Products

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

Dissecting the Product-Specific Guidance for Paliperidone Palmitate

1. Nonbinding Recommendations
2. Parallel or crossover steady state PK
3. In patient population
4. Both sites of injection
5. Individual steady state attainment



Contains Nonbinding Recommendations

Draft Guidance on Paliperidone Palmitate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Extended-release suspension; intramuscular

Recommended Studies: One study

Type of study: (1) Parallel group, steady-state or (2) two-period, crossover steady-state
Strength: 156 mg/mL
Subjects: Male and nonpregnant female patients with schizophrenia or schizoaffective disorder who are already receiving a stable regimen of paliperidone palmitate extended-release suspension via the intramuscular route. Patients who are already receiving 156 mg of paliperidone injection every month would be eligible to participate in the study if continuing their established maintenance dose.
Additional comments: (1) FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment. (2) Both sites of injection (gluteal and deltoid) should be included in the study design for adequate site representation to support the results of the study. (3) More than three doses may be required to reach steady state. Pharmacokinetic (PK) data should be submitted to demonstrate that steady state has been reached for each individual.

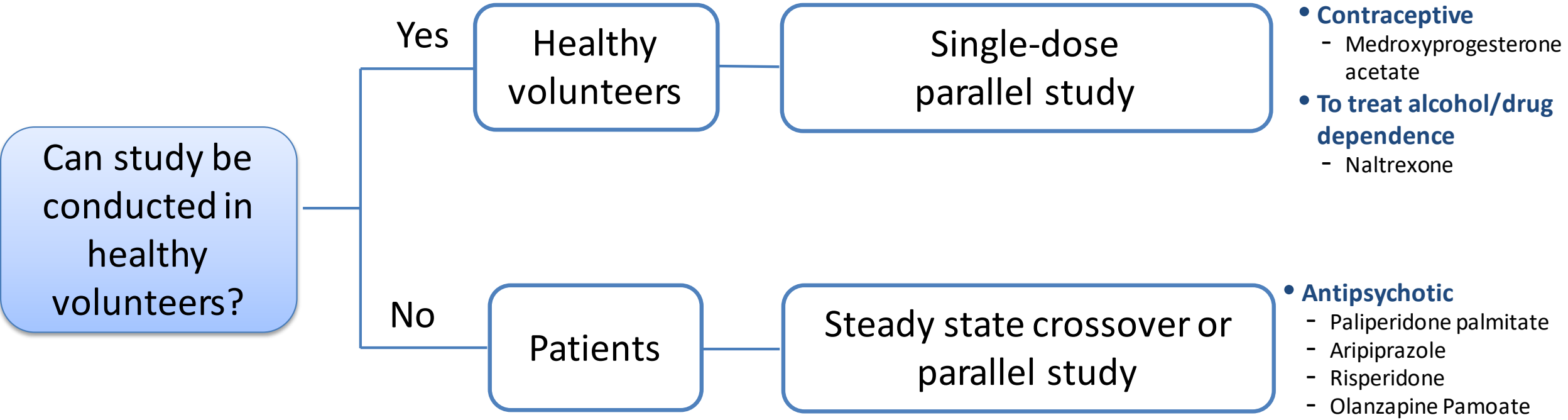
Analytes to measure (in appropriate biological fluid): Paliperidone in plasma

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Paliperidone%20palmitate%20inj%20ER%20suspension%20RLD%2022264%20RV07-16.pdf

In Vivo Study Challenges for Long-Acting Injectables

- May not be feasible in healthy volunteers due to safety
- Long duration of use
  - Not practical for cross over study design
    - Washout period for a crossover study: 5 $t_{1/2}$
    - Increased drop out
  - Long-term side effect
  - Increased variation in PK
- Larger sample size due to PK variability
- Determination of steady state

Types of BE study designs for Long-Acting Injectables (LAIs)



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

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

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

Challenges with Parallel Design

- May not be recommended due to safety concerns
- Requires larger sample size than cross-over studies
- Examples:
  - Contraceptive
    - Medroxyprogesterone acetate
  - To treat alcohol/drug dependence
    - Naltrexone

Challenges with Crossover Study Designs

- Steady state studies lead to extremely long study durations
- Patient population
- Steady state determination can be challenging
- Examples
  - Antipsychotic
    - Paliperidone palmitate
    - Aripiprazole
    - Risperidone
    - Olanzapine Pamoate

Model Integrated Evidence

- **Model-informed drug development (MIDD)** under the Prescription Drug User Fee Amendments of 2017 (PDUFA VI)
  - To inform drug development and regulatory decision makings by using population PK, dose/exposure–response relationships, and biological and statistical models derived from preclinical and clinical data sources
- **Model-based approach**
  - To include modeling and simulation in development and decision making
- **Model integrated evidence (MIE)** refers to using MIE such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence for the following
  - Support product approval
  - In combination with relevant *in vitro* BE testings, support alternatives to otherwise recommended conventional *in vivo* BE studies, including but not limited to PK, PD, or comparative clinical endpoint BE studies

Clin Pharmacol Ther. 2019 Feb;105(2):338-349

Qualifications of Using Model Integrated Evidence

- Sufficiently verify and validate the model for the purpose of use
- Should have acceptable Type I error
- Can have higher power than NCA-based method to pass good products
- Reduce study sample size and duration

NCA: non-compartmental analysis

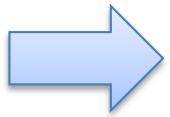
Glean the Benefit of Modeling and Simulation (M&S)

Model-informed approach

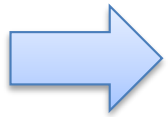
To modify NCA-based BE methods for LAI

Model-based/integrated approach

To include M&S generated data in LAI BE evaluation



Reduce sample size and/or reduce study duration



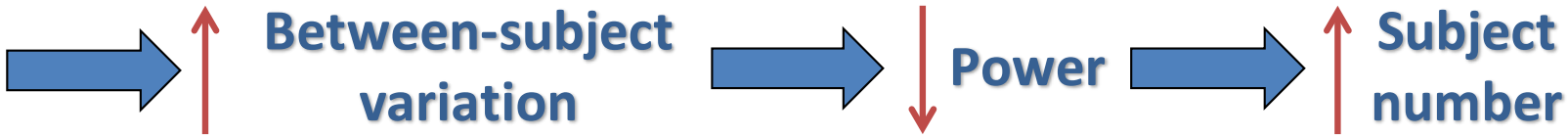
Make LAI BE study more feasible

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

Modeling Approach: Single-dose Parallel BE Study

Factors Contributing to Variability

- Body Mass Index
- Sex
- Age
- Injection site
- Others



Multiple Covariates Affects LAI Absorption, Increasing Variation

Modeling Solution to increase power to reduce sample size:

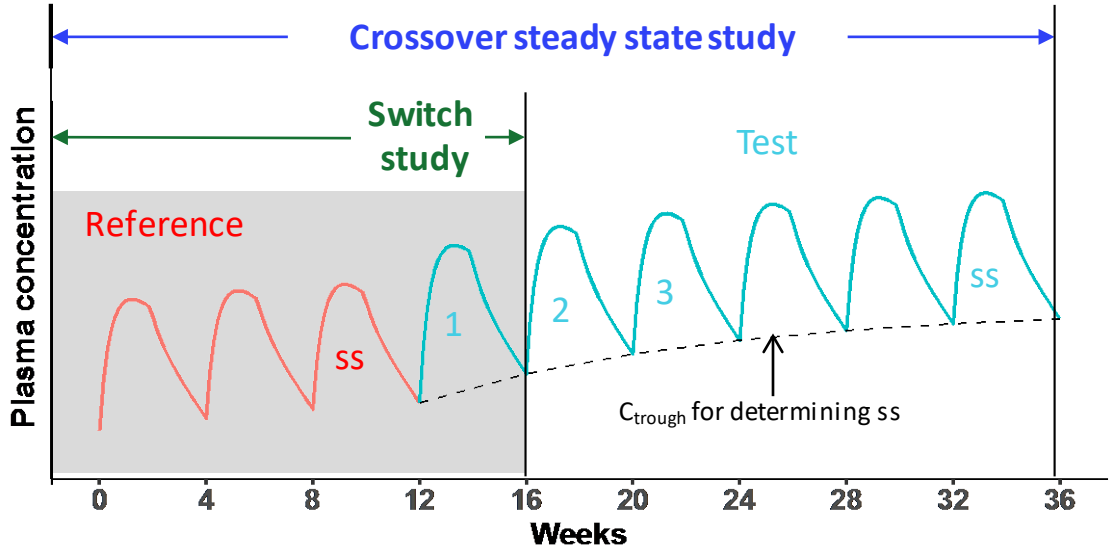
$$\log(AUC)_i = \mu + formulation + other\ covariates + \varepsilon_i$$

The equation can be developed from prior knowledge on PK information of the LAI product
Virtual simulation can be conducted to potentially support BE evaluation

Modeling Approach: Multiple Dose Crossover BE Study

Three Key Questions:

- How to determine the attainment of steady state?
- What PK metrics will lead to good BE assessment?
- What BE acceptance criteria are appropriate?



To cut cost and development time for LAI generic products, how can model-informed and based approach and model integrated evidence play a role?

Gleaning the Benefit of Modeling & Simulation

Model-informed approach

The analysis is based on NCA, not including PK modeling

Single-dose parallel study

$$\log(AUC)_i = \mu + formulation + other\ covariates + \varepsilon_i$$

M&S

Multiple-dose crossover study

Crossover ss study
Required BE criteria → Switch study
Novel BE criteria

M&S

Model-based approach + Model Integrated Evidence

The analysis include PK modeling

Data

↓

Modeling

↓

Simulation

Virtual study simulations for clinically relevant PK metrics

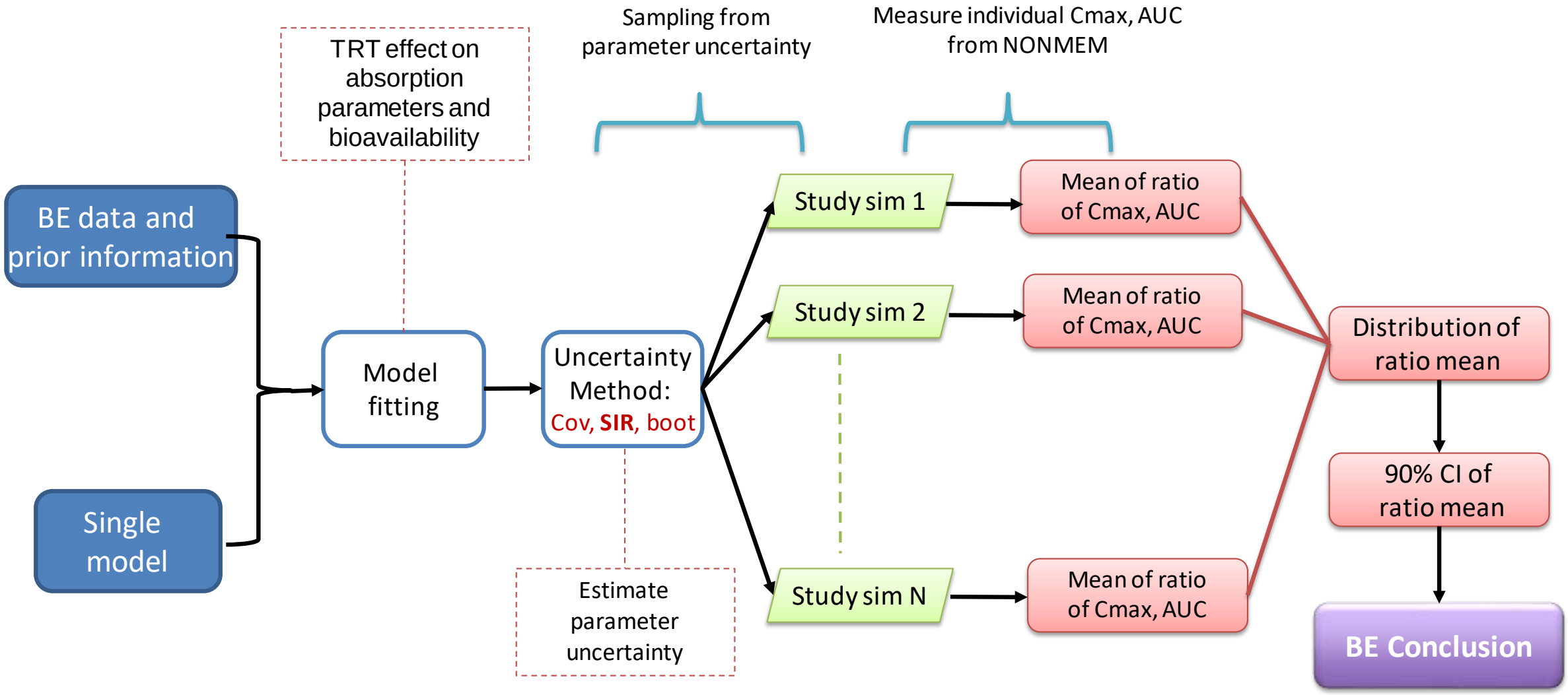
↓

Conclusion

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

Proposed Model-based BE Method Application

by Mats Karlsson



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

Regulatory Considerations for Using MIE

- Appropriate control of type 1 (from the agency) and type 2 errors
  - Sensitive to detect formulation difference
  - Reasonable passing rate for BE products
- Sufficient model verification and validation for the intended regulatory use
  - Characterization of uncertainty
  - Capable to discern formulation difference
- Modeling analysis plan prior to seeing study results
  - Communication with the agency via Controlled Correspondence or Pre-ANDA interactions (https://www.fda.gov/drugs/generic-drugs/pre-anda-program)

List of FDA funded M&S Grants/Contracts for LAI Products

Project title	Study duration	Grantee/Contractor	Grant/Contract No.
Development of model-informed bioequivalence evaluation strategies for long-acting injectable products	2019-2021	Uppsala University	75F40119C10018
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

Welcome to propose and submit proposals to advance regulatory science.

GDUFA Regulatory Science: https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-regulatory-science

Further Research on MIE Warranted

- Extrapolate sufficiently verified and validated models to other BE study design scenarios
- Use models built on a small sample size to simulate results from a larger population
- Use models to inform more efficient study design and BE evaluation criteria
- Use Physiologically Based PK/mechanistic models to inform in vitro BE method development (not covered in this talk)
- *Note: none of the model based or model integrated approaches need individual steady state evaluation*

Conclusions

- Model-based BE assessment and MIE can significantly cut cost and time of LAI generic product development
  - Reduced sample size
  - Reduced time line
  - No individual steady state evaluation
- Novel modeling analysis plan need to be communicated with the FDA before implementation via pre-ANDA interactions

Acknowledgements

FDA/CDER/OGD/ORS

- Lucy Fang, Ph.D.
- Satish Sharan. Ph.D.
- Yan Wang, Ph.D.
- Bin Qin, Ph.D.
- Robert Lionberger, Ph.D.

Uppsala University

- Mats Karlsson, Ph.D.
- Xiaomei Chen, Ph.D.
- Andrew Hooker, Ph.D.

All grantees