Application of Quantitative Clinical Pharmacology in the Development of Long-Acting Injectable (LAI) Drug Products

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

The New York Times

PERSONAL HEALTH

The Cost of Not Taking Your Medicine

Paul Rogers

- Poor adherence to prescribed medications significantly impacts the U.S. health care system.
- Given the human and financial consequences, the development of strategies for improving adherence to prescribed medications is imperative.
- Long-acting injectable (LAI) drug products are one of several interventions for improving patient adherence to prescription medications.

https://www.nytimes.com/2017/04/17/well/the-cost-of-not-taking-your-medicine.html
Sharan et al. 2021, CPDD 10(3): 220-228

Long-Acting Injectable Drug Products

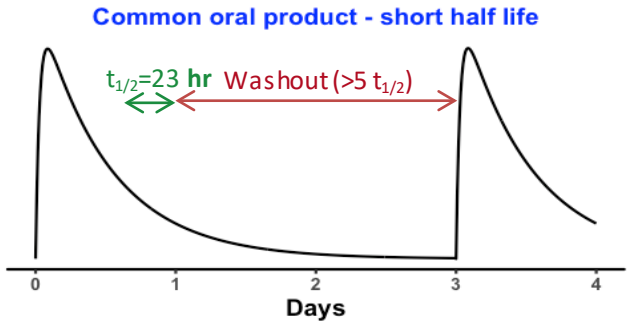
- Long-acting injectable (LAI) drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular (IM) and subcutaneous (SC) routes.

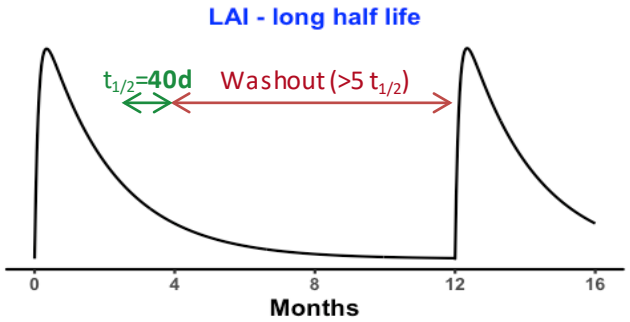
- These products can help improve patient compliance with a better therapeutic option to treat patients who adhere poorly to frequently administered medication.

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

Long-Acting Injectable Pharmacokinetics





- LAI pharmacokinetics (PK) are characterized by a rate of drug absorption that is slower than their rate of elimination; hence, they exhibit flipflop kinetics.
- In these products, the terminal phase of the drug profile reflects the rate of absorption, rather than the rate of elimination, as is usually observed in classical linear drug PK.
- The long terminal phase of these products poses several challenges for the development of new versions, as well as generic copies.

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

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

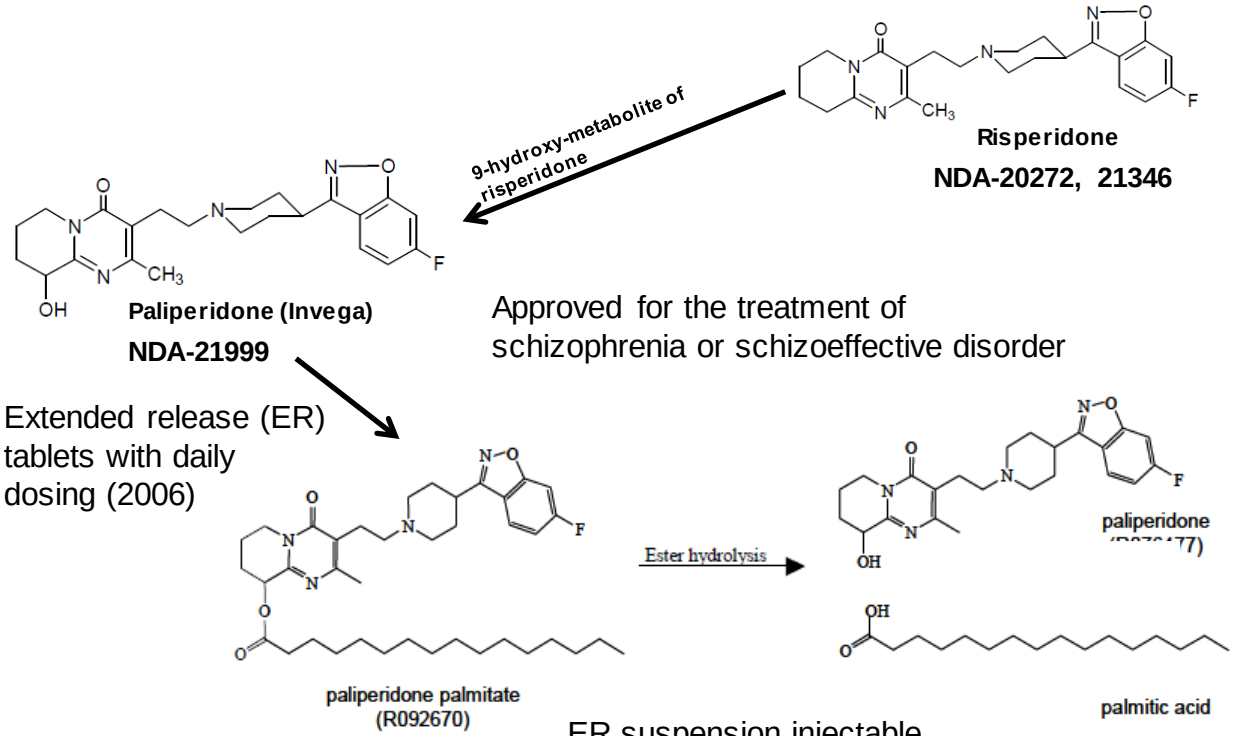
Opportunities for Modeling and Simulation in LAI Product Development

- 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

Opportunities for Modeling & Simulation in Life Cycle Management

- Optimize BE study design
- Sample size
- Simulate bio-inequivalent scenarios
- Design/justify a shorter duration BE study

Example: Paliperidone; Paliperidone Palmitate



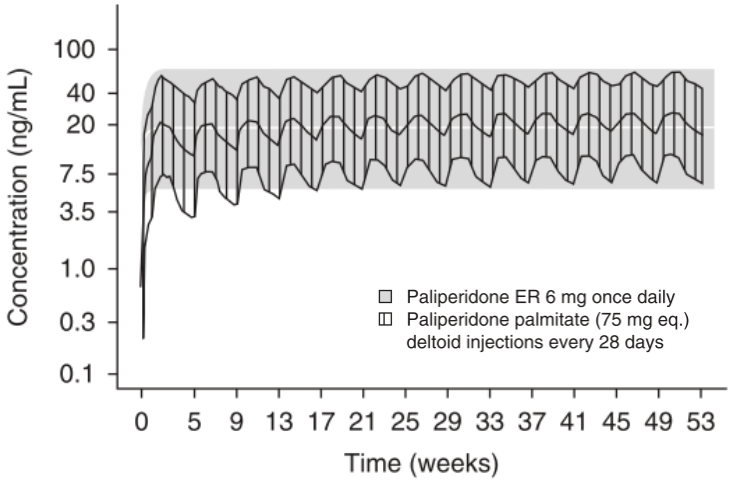
INVEGA SUSTENNA Background

- Invega Sustenna is an atypical antipsychotic administered monthly for:
  - Treatment of schizophrenia in adults
  - Treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants

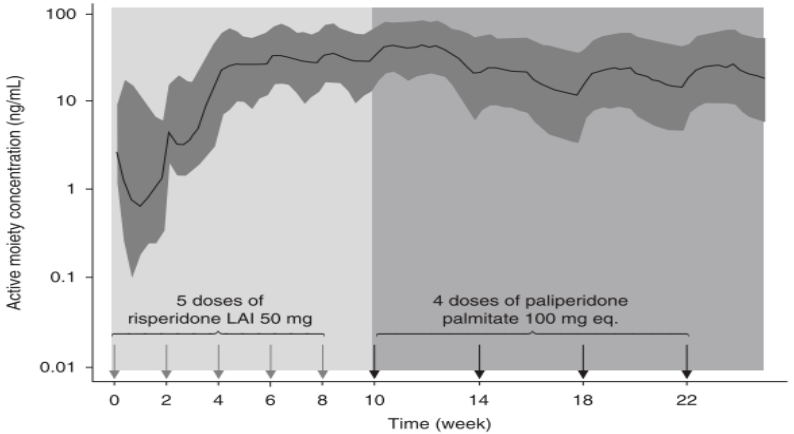
Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia	234 mg (150 mg eq.)	156 mg (100 mg eq.)	39 (25 mg eq.) - 234 mg (150 mg eq.)	234 mg (150 mg eq.)
Schizoaffective disorder	234 mg (150 mg eq.)	156 mg (100 mg eq.)	78 mg (50 mg eq.) - 234 mg (150 mg eq.)	234 mg (150 mg eq.)

Application of Quantitative Clinical Pharmacology in New Drug Development

Dosing Regimen Based on Comparable Exposure



Switch Between Risperidone LAI to PP1M



Modeling & Simulation has been effectively used to support development of LAI drug products.

Samtani, et.al , CNS Drugs 2011

Clinical pharmacology review for Invega Sustenna at Drug@FDA

Product-Specific Guidance (PSG)

- FDA publishes PSGs to facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval.

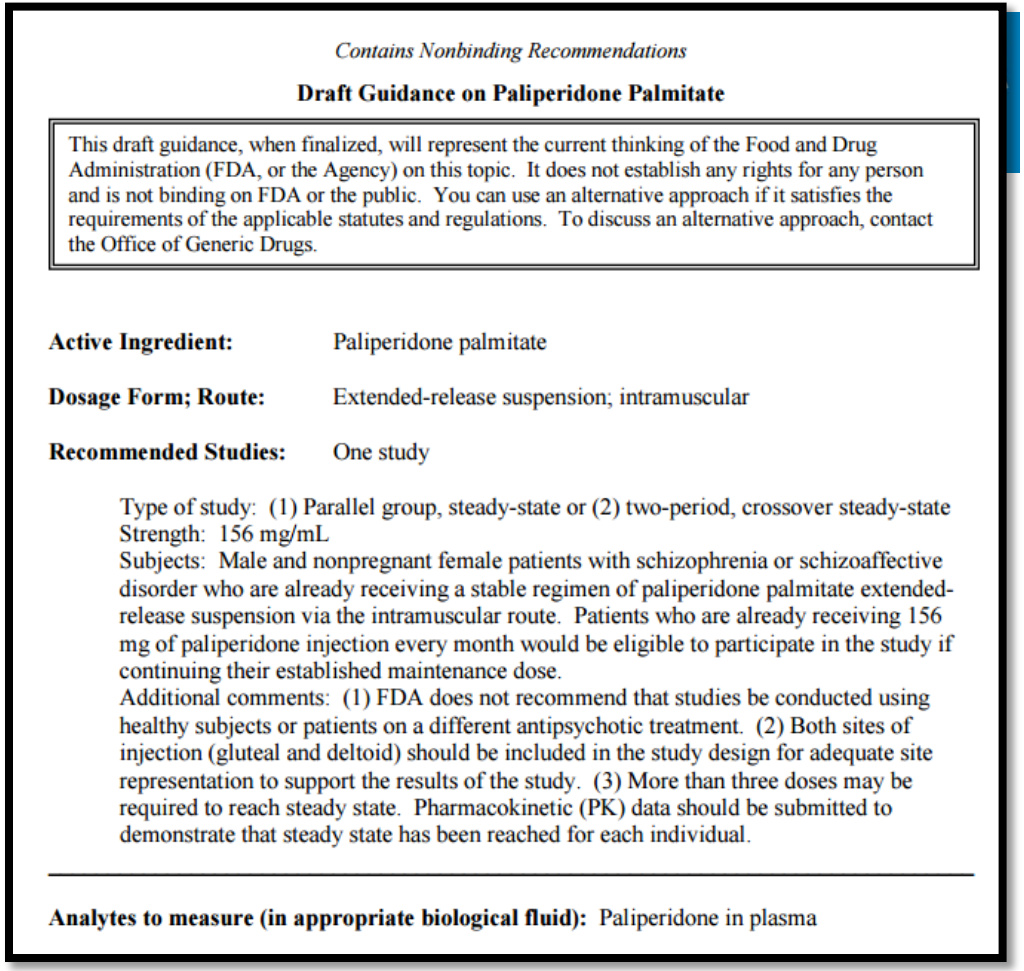
- PSGs describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent (TE = PE + BE) to specific reference listed drugs.

- For two products to be considered bioequivalent, there should be no significant difference in the rate and extent of absorption of the active moiety, which are usually measured by Cmax (the maximum drug concentration) and AUC (the area under the concentration-time curve), respectively.

PE = Pharmaceutically Equivalent
FDA Product-Specific Guidance Webpage: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

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

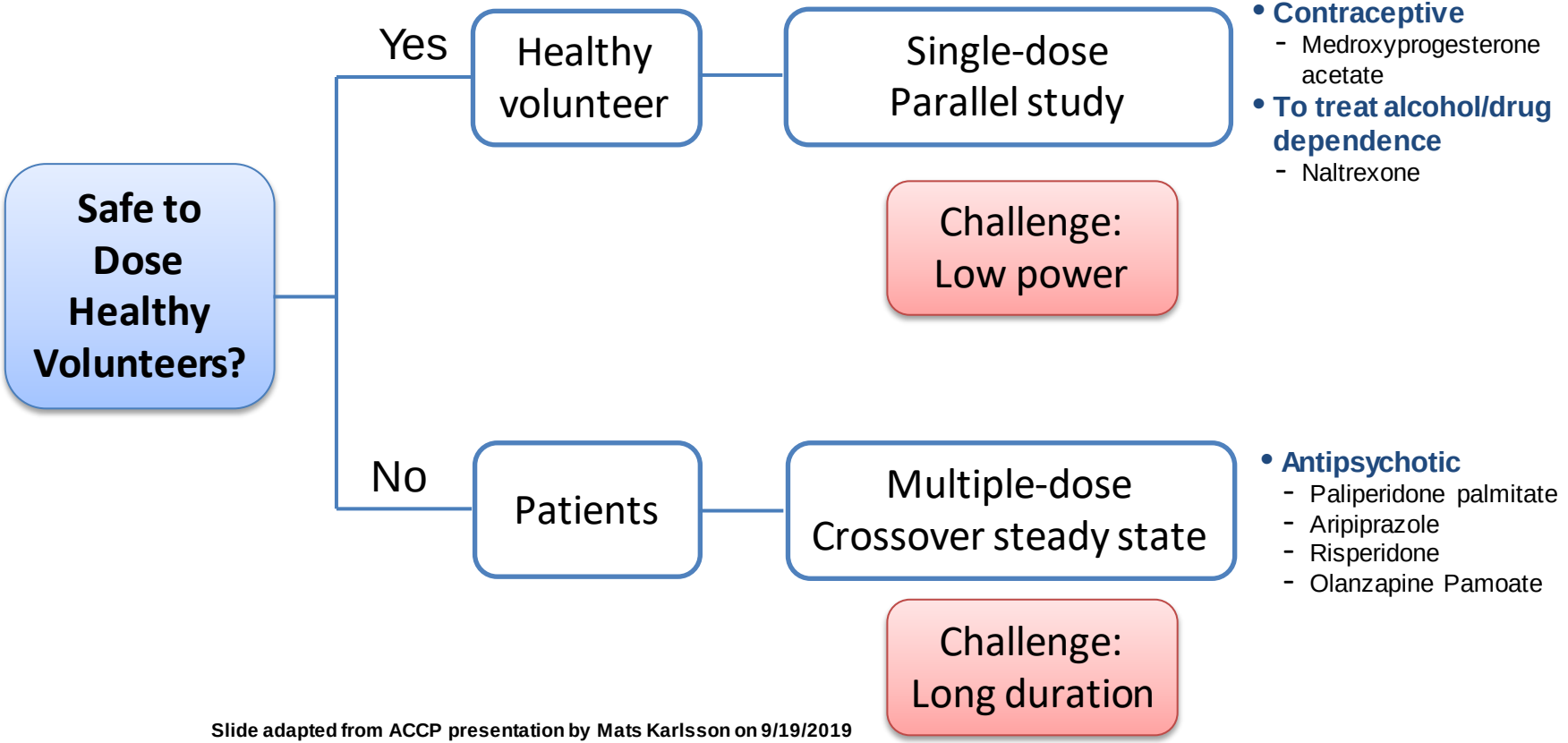
Recommended Studies: One study

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

Types of BE Study Designs for LAI Products



- **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

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 models not just to plan a pivotal study but to serve as pivotal evidence
  - Support product approval via a prespecified model based analysis of an in vivo BE study
  - Support product approval via a virtual bioequivalence (VBE) study
  - In combination with relevant *in vitro* BE tests, support alternatives to otherwise recommended *in vivo* BE studies, including but not limited to PK, pharmacodynamics (PD), or comparative clinical endpoint BE studies

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

Considerations for Using Model Integrated Evidence

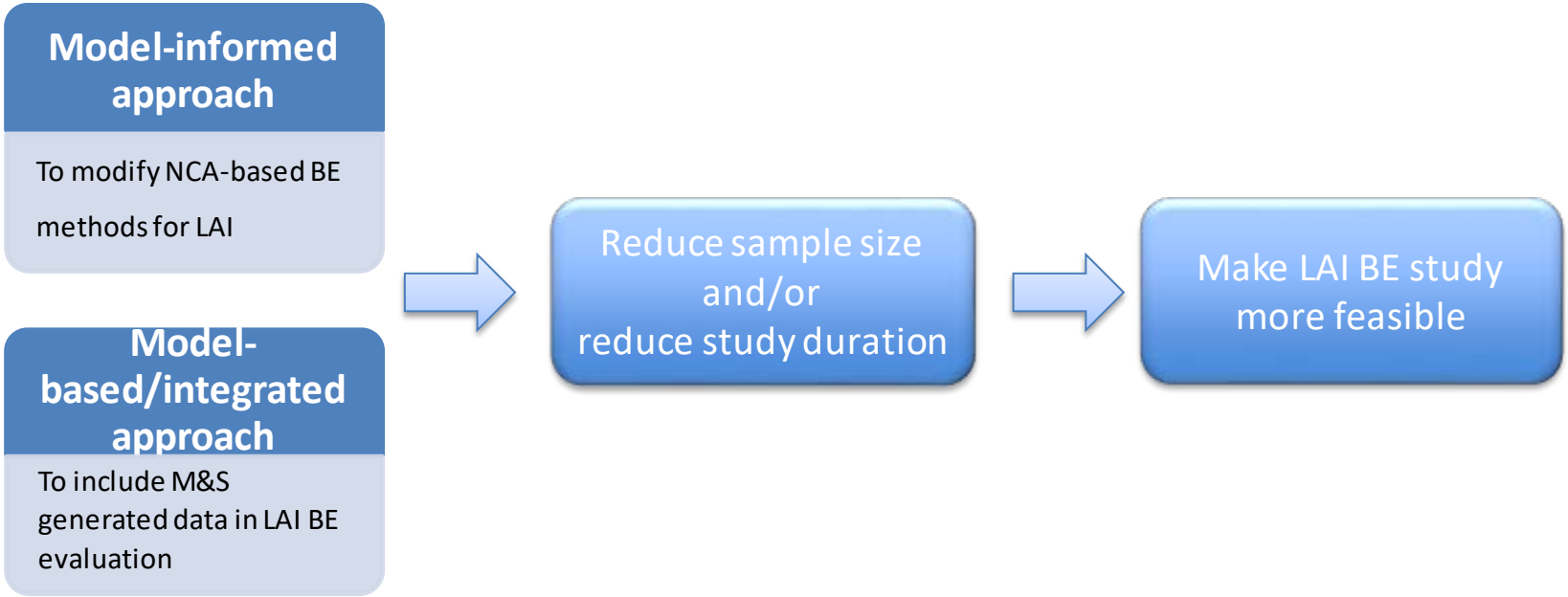
- Verify and validate the model for the purpose of use
- Demonstrate acceptable Type I error

Advantages of Using Model Integrated Evidence

- Higher power than NCA-based method to pass BE products
- Reduce study sample size and duration

NCA: non-compartmental analysis

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

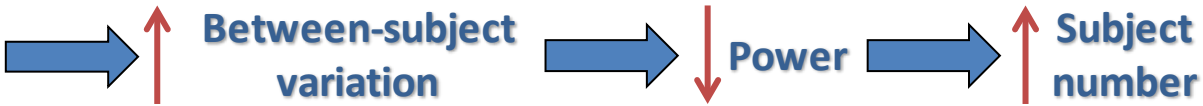


Modified from ACCP presentation by Mats Karlsson on 9/19/2019

Modeling Approach: Single-dose Parallel BE Study

Factors Contributing to Variability

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



Multiple Covariates Affect LAI Absorption, Increasing Variation

Modeling solution to increase power to reduce sample size:

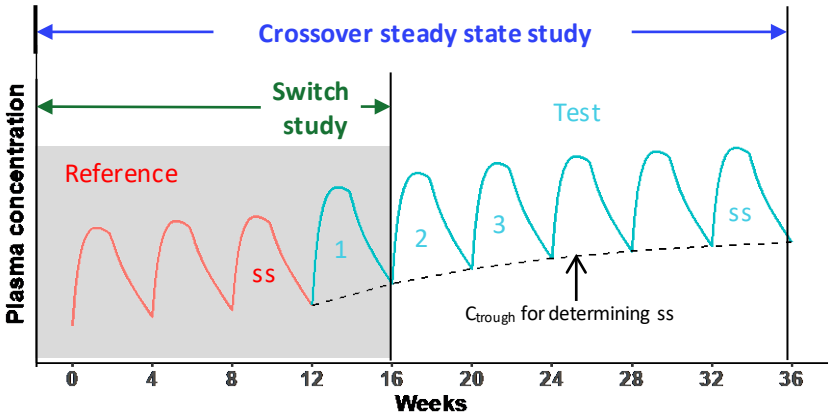
$$\log(AUC)_i = \mu + formulation + other\ covariates + \varepsilon_i$$

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 BE 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 → Switch study

Inform novel BE criteria

M&S

Model-based approach + Model integrated evidence (MIE)

The BE analysis includes PK modeling

Data from BE study

↓

Pre-specified Model

↓

Simulation

Virtual study simulations for clinically relevant PK metrics

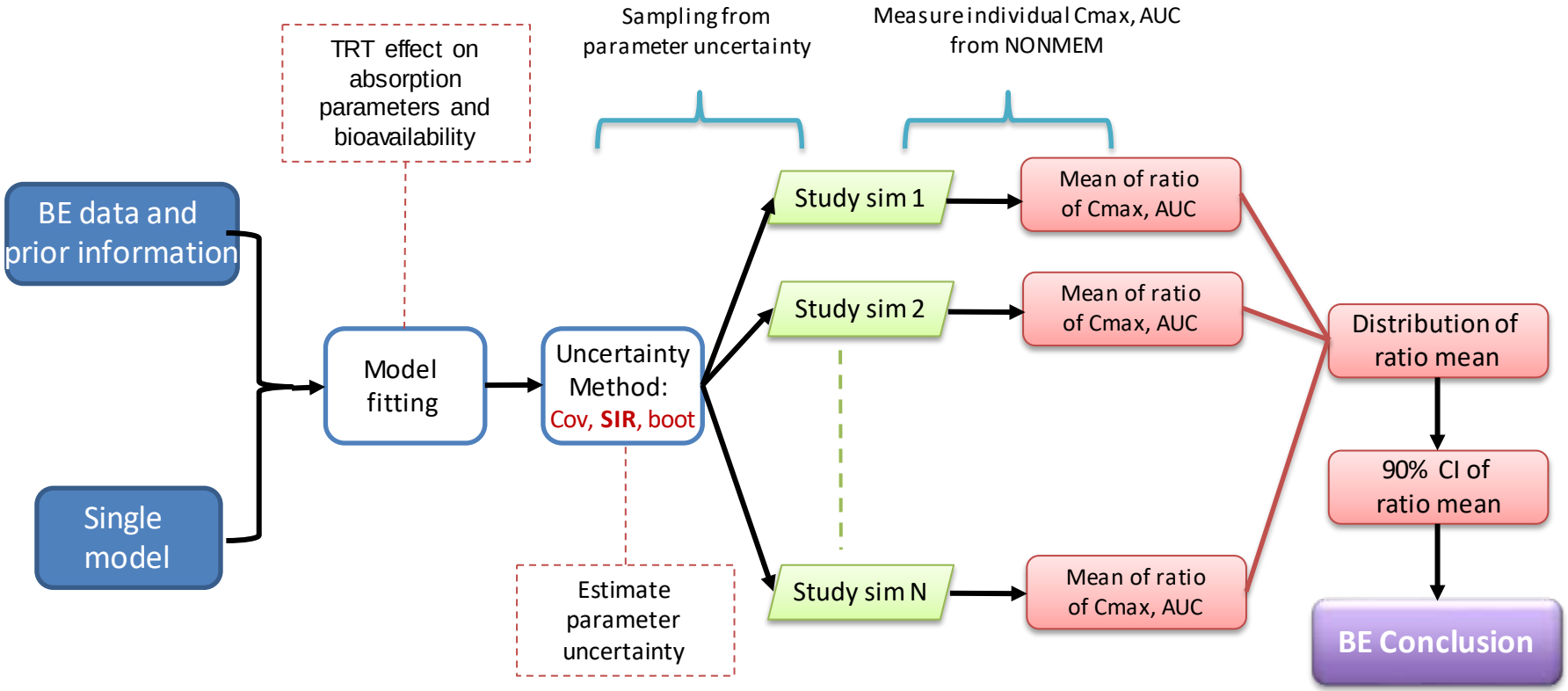
↓

Conclusion

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

Proposed Model-based BE Method Application

by Mats Karlsson



TRT = Treatment

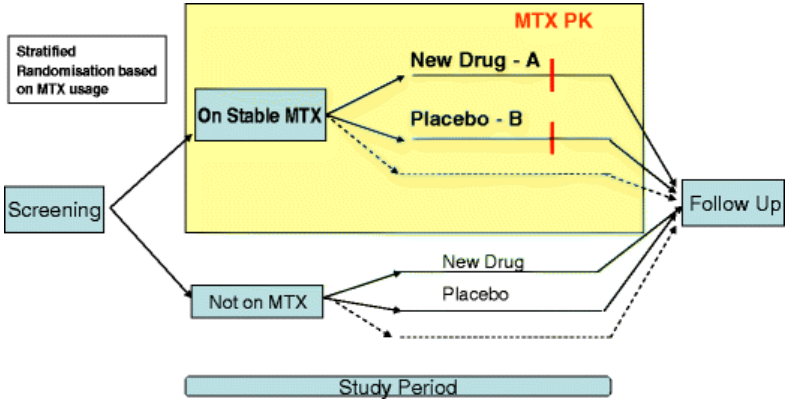
Modified from ACCP presentation by Mats Karlsson on 9/19/2019

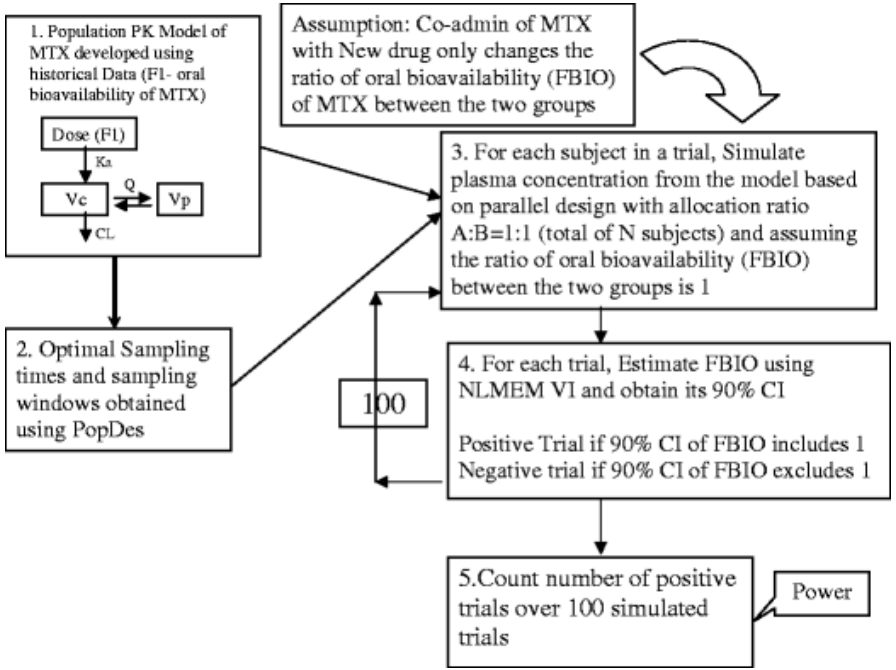
Another Look at the Model-Based Approach

- Can the evaluation method be more convenient and simple?
- Can we allow less samples per subject?
- Can we take a hybrid approach?
  - E.g., use actual observation for Cmax and modeling for AUC?
- Can we make the study shorter?
  - E.g., can we use non steady state data to do the assessment?

Insight gained in using modeling approach to assess drug-drug interaction (DDI)

Population PK Based Approaches to Evaluation Drug-Drug Interaction (1)

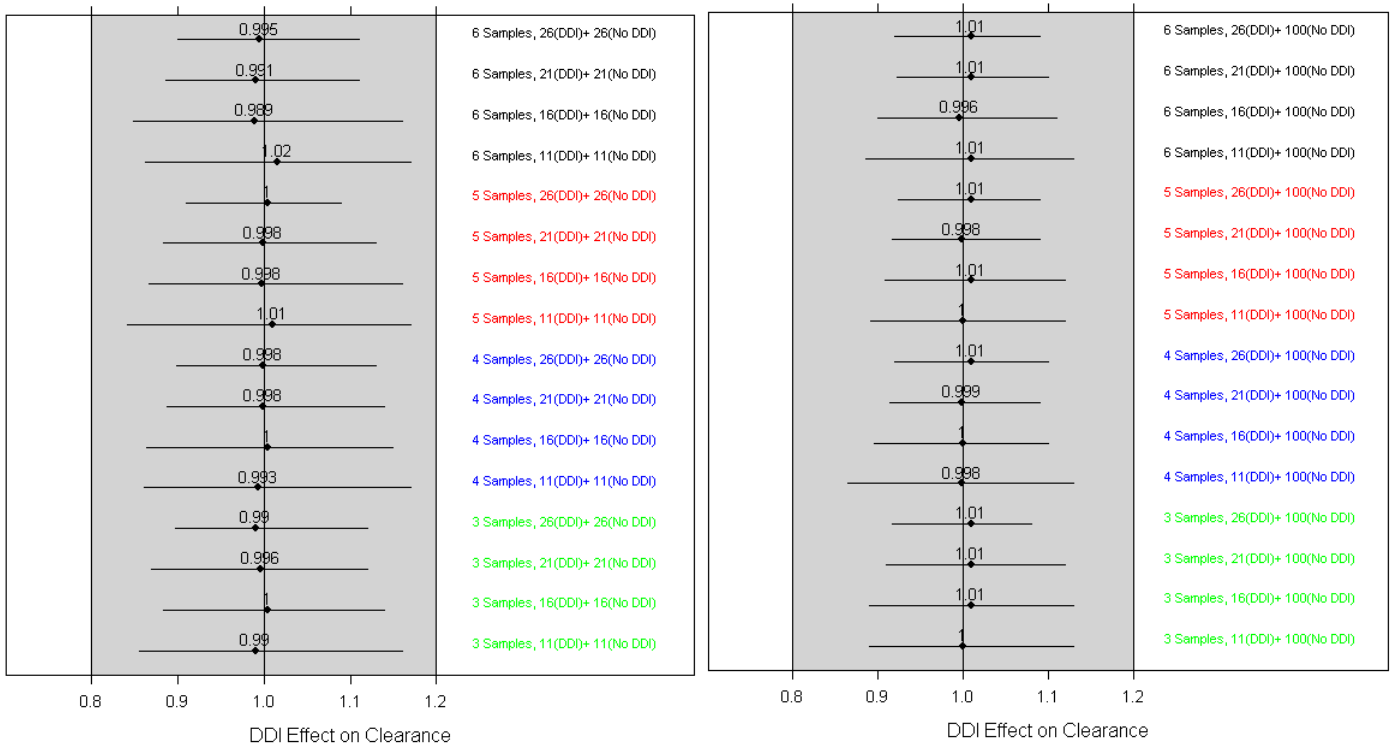




European Journal of Clinical Pharmacology volume 67, 225–233(2011)

Population PK Based Approaches to Evaluation Drug-Drug Interaction (2)

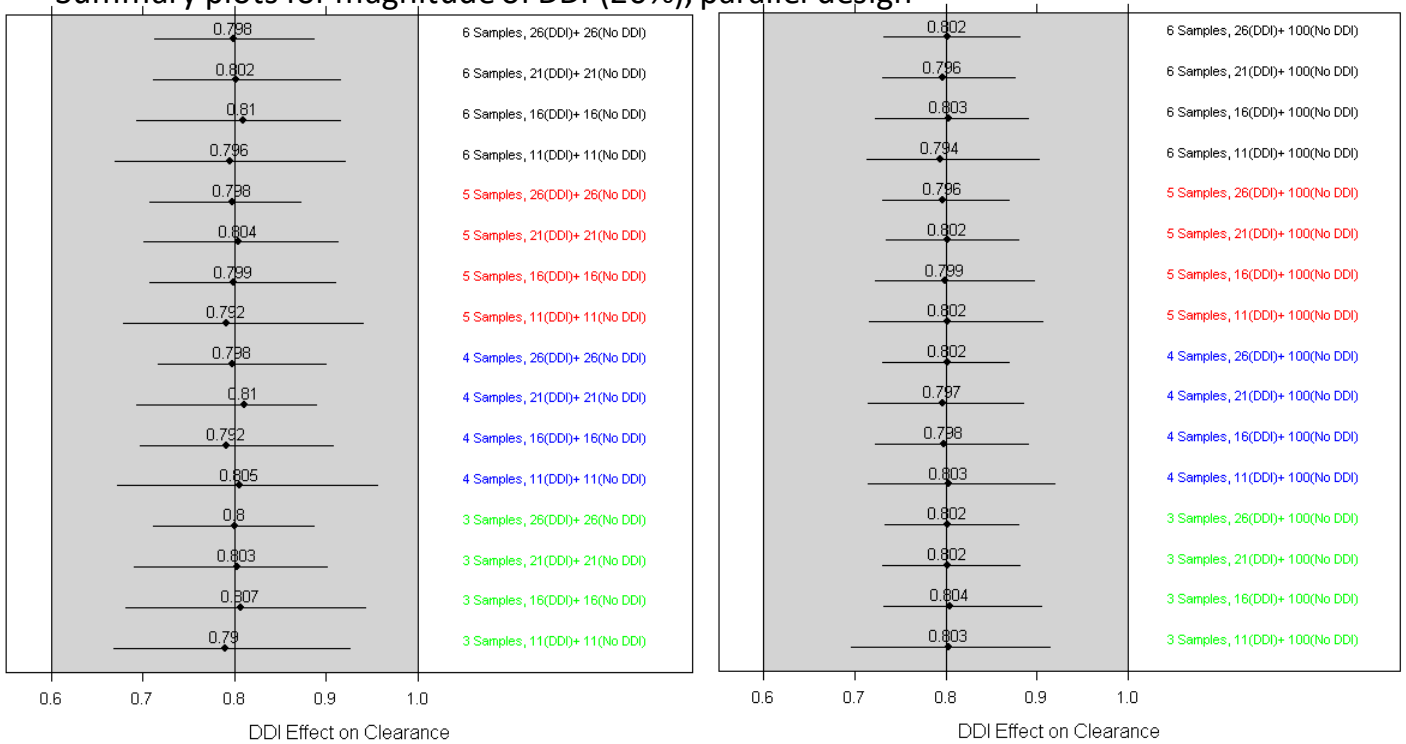
Summary plots for magnitude of DDI (0%), parallel design



J Clin Pharmacol. 2017 Oct;57(10):1268-1278

Population PK Based Approaches to Evaluation Drug-Drug Interaction (2)

Summary plots for magnitude of DDI (20%), parallel design



J Clin Pharmacol. 2017 Oct;57(10):1268-1278

Findings from DDI Evaluations

- The magnitude of the DDI effect was well estimated without bias
- PopPK approach could achieve reasonable power with adequate study designs
- The number of subjects appears to have a larger effect on power than the number of samples per subject
- DDI evaluation for drugs with longer half-life and less fluctuation is more resistant to sampling or dosing time error
- Structural model misspecification had limited impact on the DDI assessment with the PopPK approach

Regulatory Considerations for Using MIE

- Appropriate regulatory standards
  - Sensitive to detect formulation difference (related to type 1 error)
  - Reasonable passing rate for BE products (related to type 2 error)
- 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 is 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 needs individual steady state evaluation*

Conclusions

- Model-based BE assessment and MIE can cut cost and time of LAI generic product development
  - Reduced sample size
  - Reduced time line
  - No individual steady state evaluation

- Novel modeling analysis plan should be communicated with the FDA before implementation via pre-ANDA interactions

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Uppsala University

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