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

ACCP:

Applying Pharmacometrics to Precision Dosing in the Lifecycle of Long-acting Injectable Products: Drug Development, Regulatory Approval & Clinical Practice

September 21, 2020

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Disclaimer

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

Long-Acting Injectable Drug Products

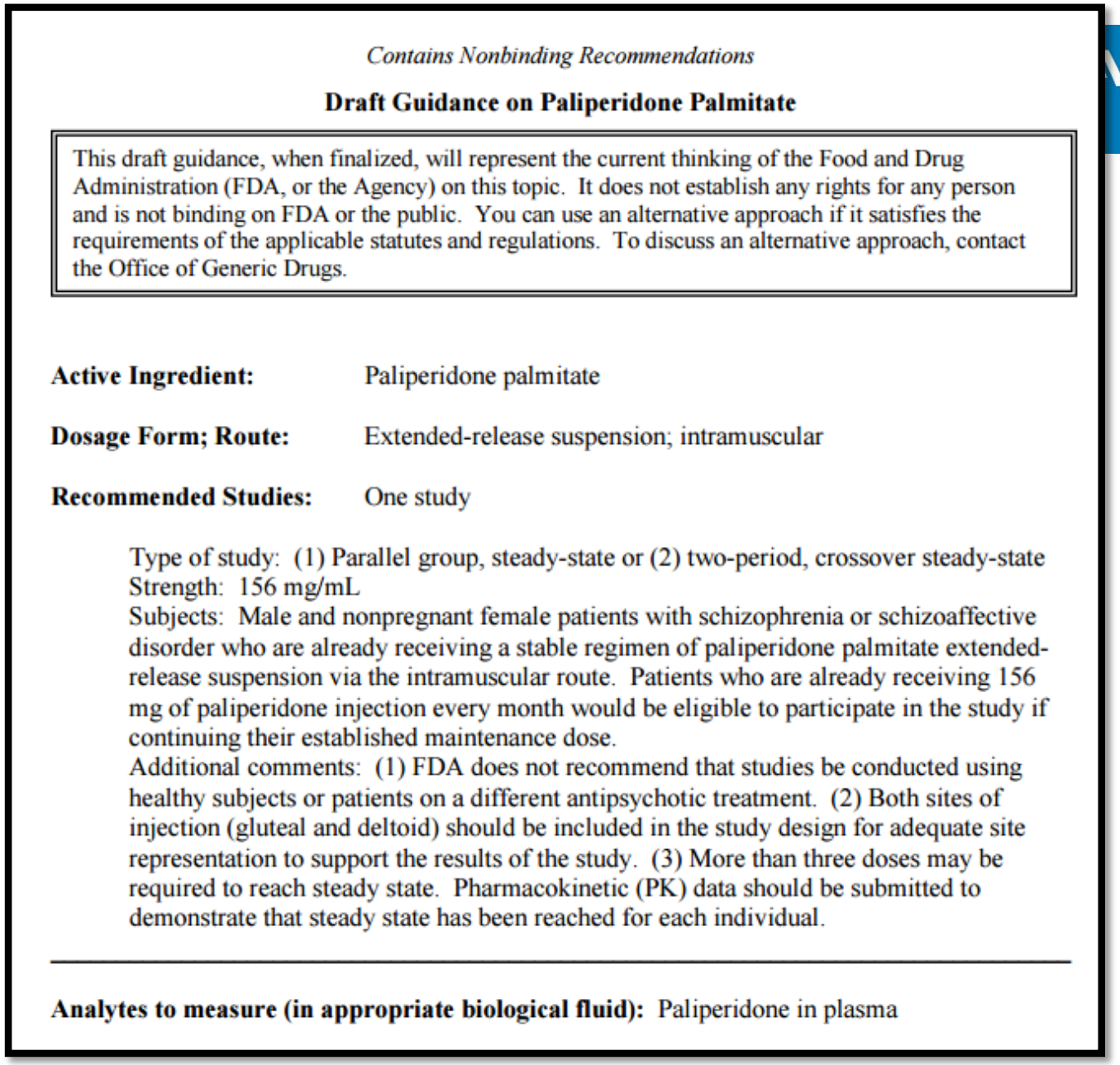
- Long-acting injectable (LAI) drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular, subcutaneous, intravitreal, or other routes.
- These products can help improve patient compliance with a better therapeutic option to treat patients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

Examples of FDA Approved Long-Acting Injectable Drug Products

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

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.

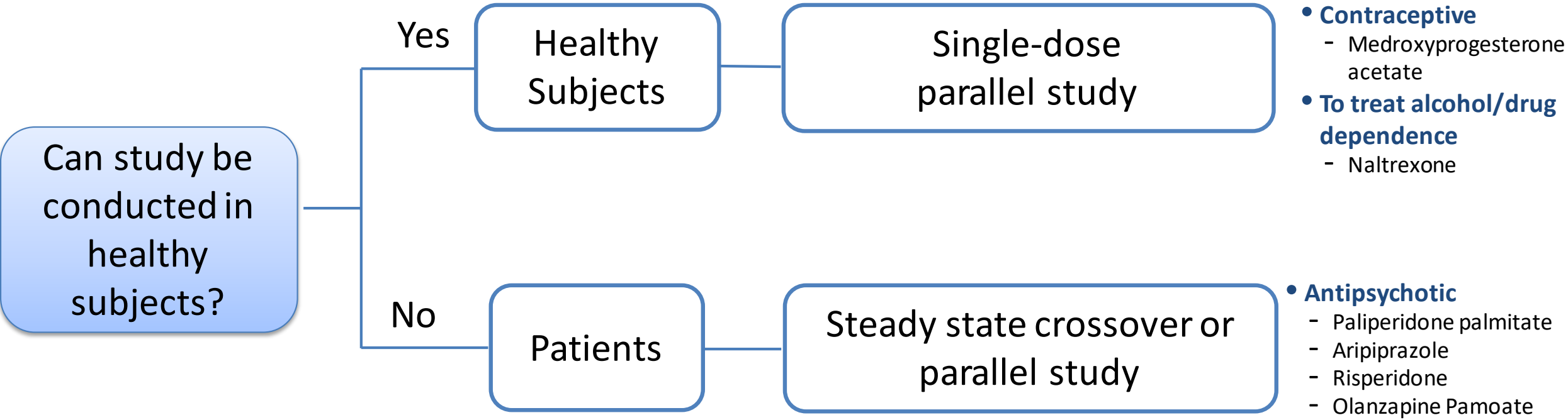
Analytes to measure (in appropriate biological fluid): Paliperidone in plasma

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 subjects 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 Bioequivalence (BE) Study Designs for Long-Acting Injectables (LAIs)



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

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

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 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

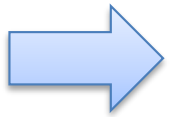
Gleaning the Benefit of Modeling and Simulation (M&S)

Model-informed approach

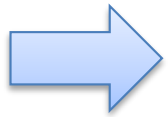
To modify NCA-based BE methods for LAI

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

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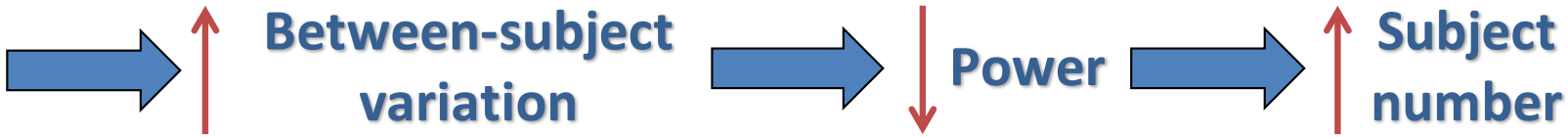
Modeling Approach: Single-dose Parallel BE Study

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:

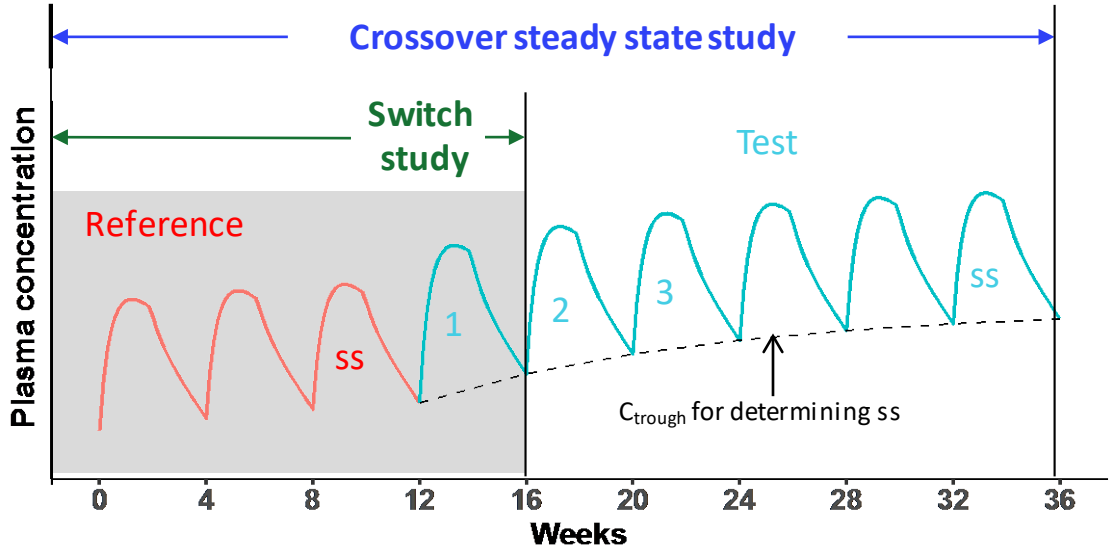
$$\log(AUC)_i = \mu + formulation + other\ covariates + \varepsilon_i$$

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

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Simulation

Virtual study simulations for clinically relevant PK metrics

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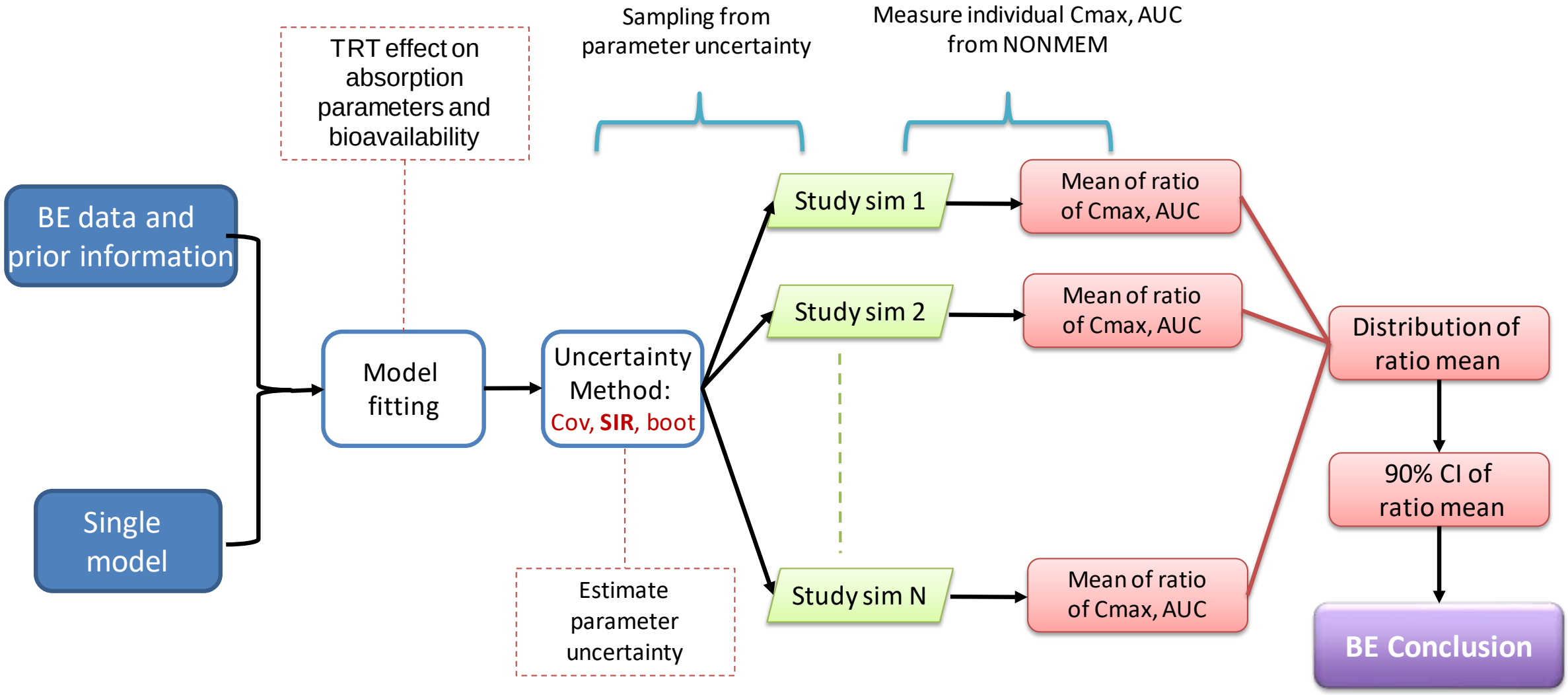
Conclusion

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

Proposed Model-based BE Method Application

by Mats Karlsson



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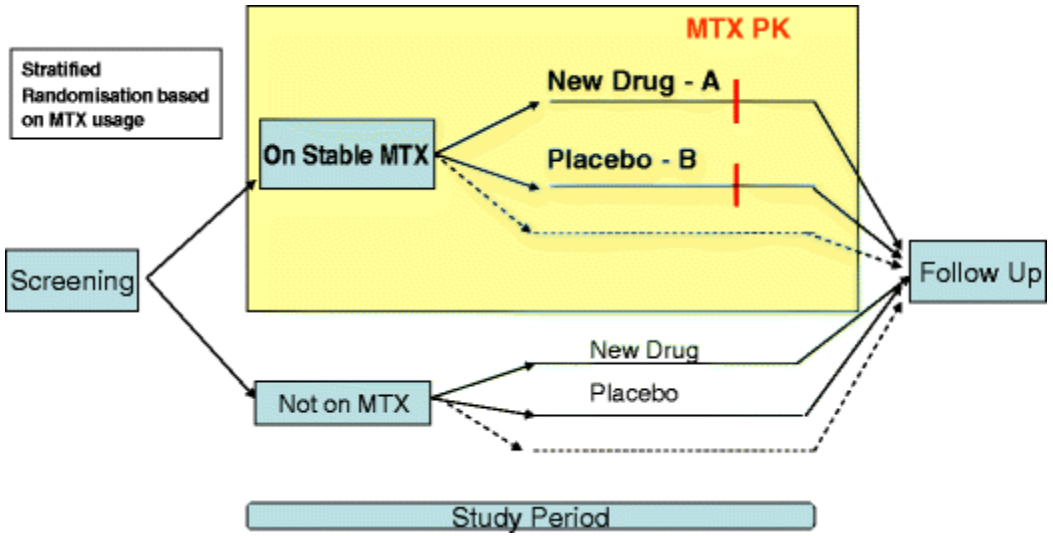
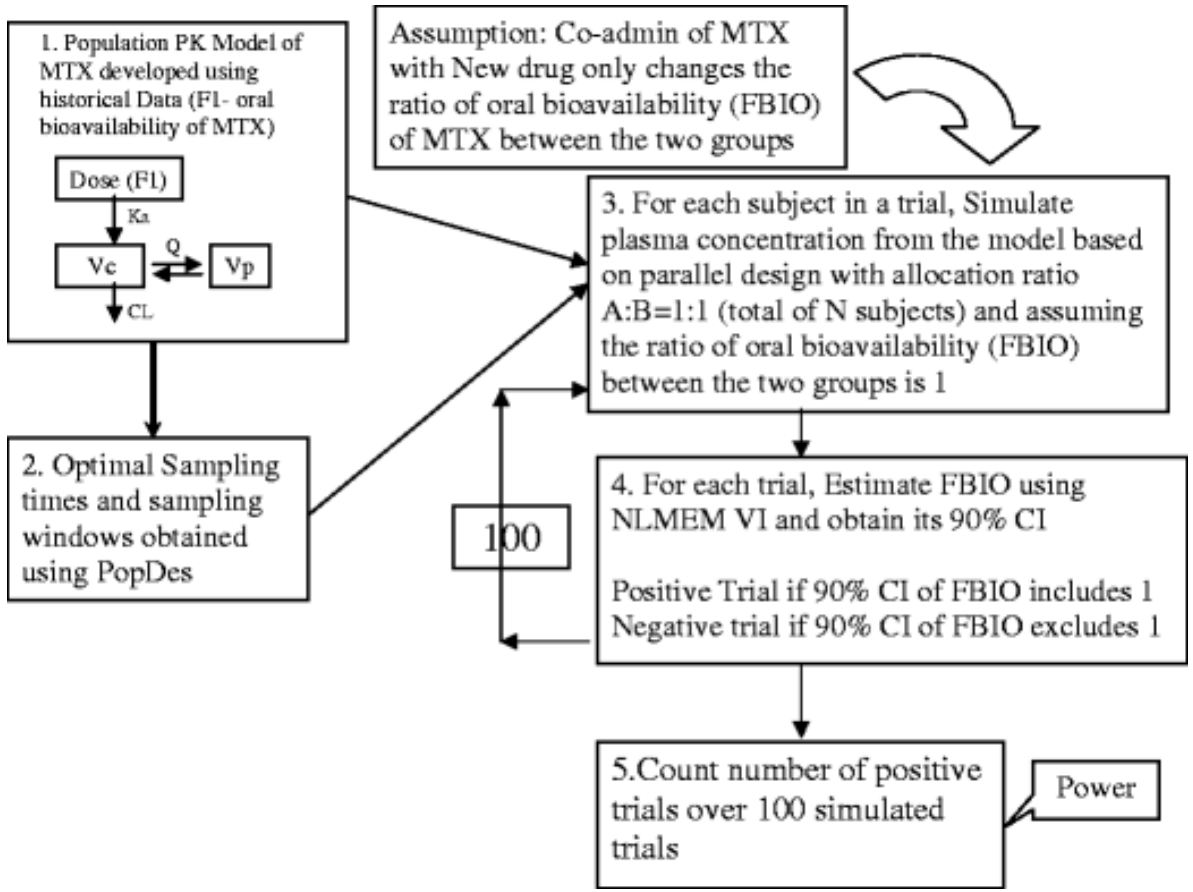
Another Look at the Model-Based Approach

- 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)

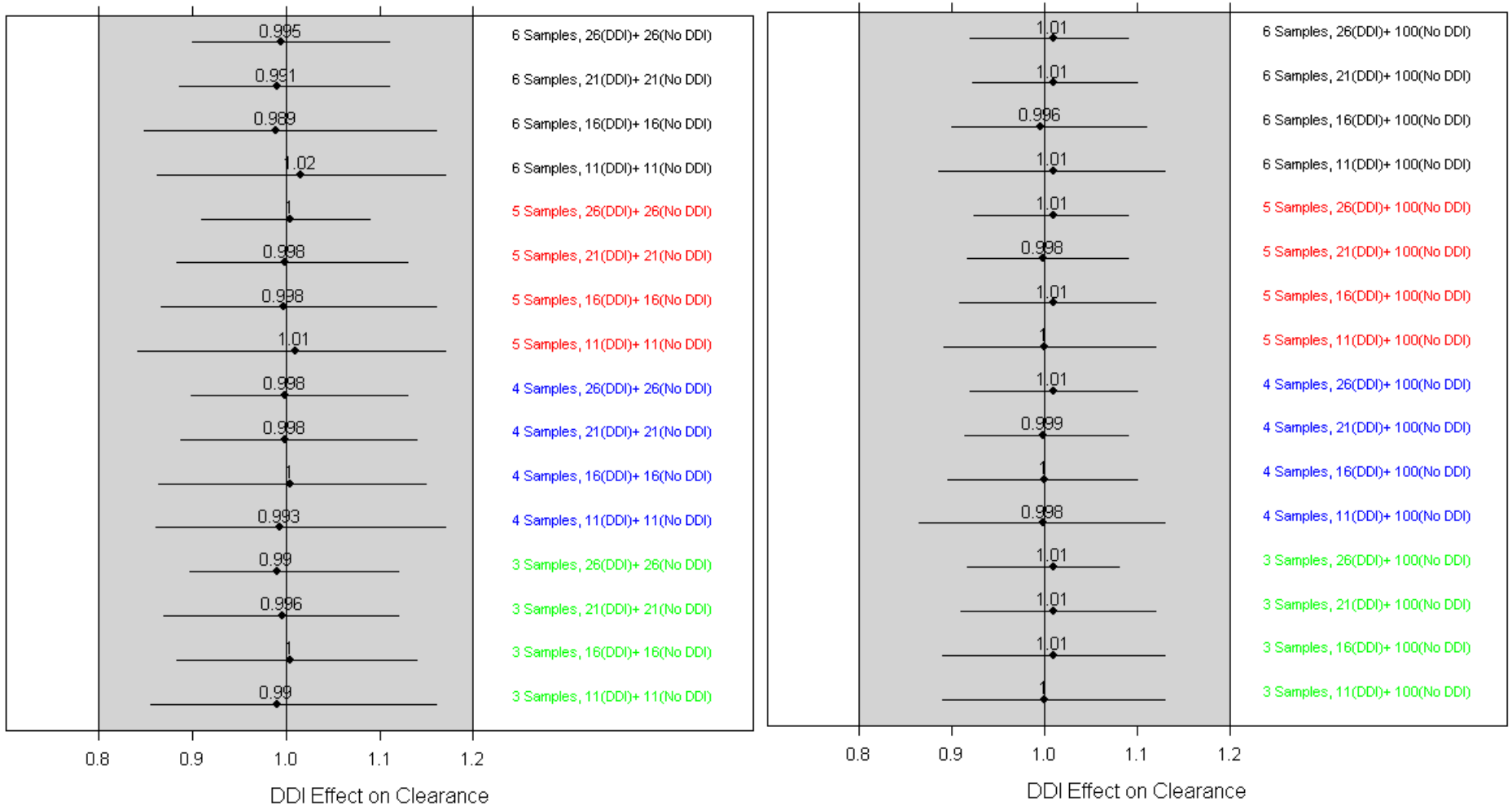




European Journal of Clinical Pharmacology volume 67, 225–233(2011)

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

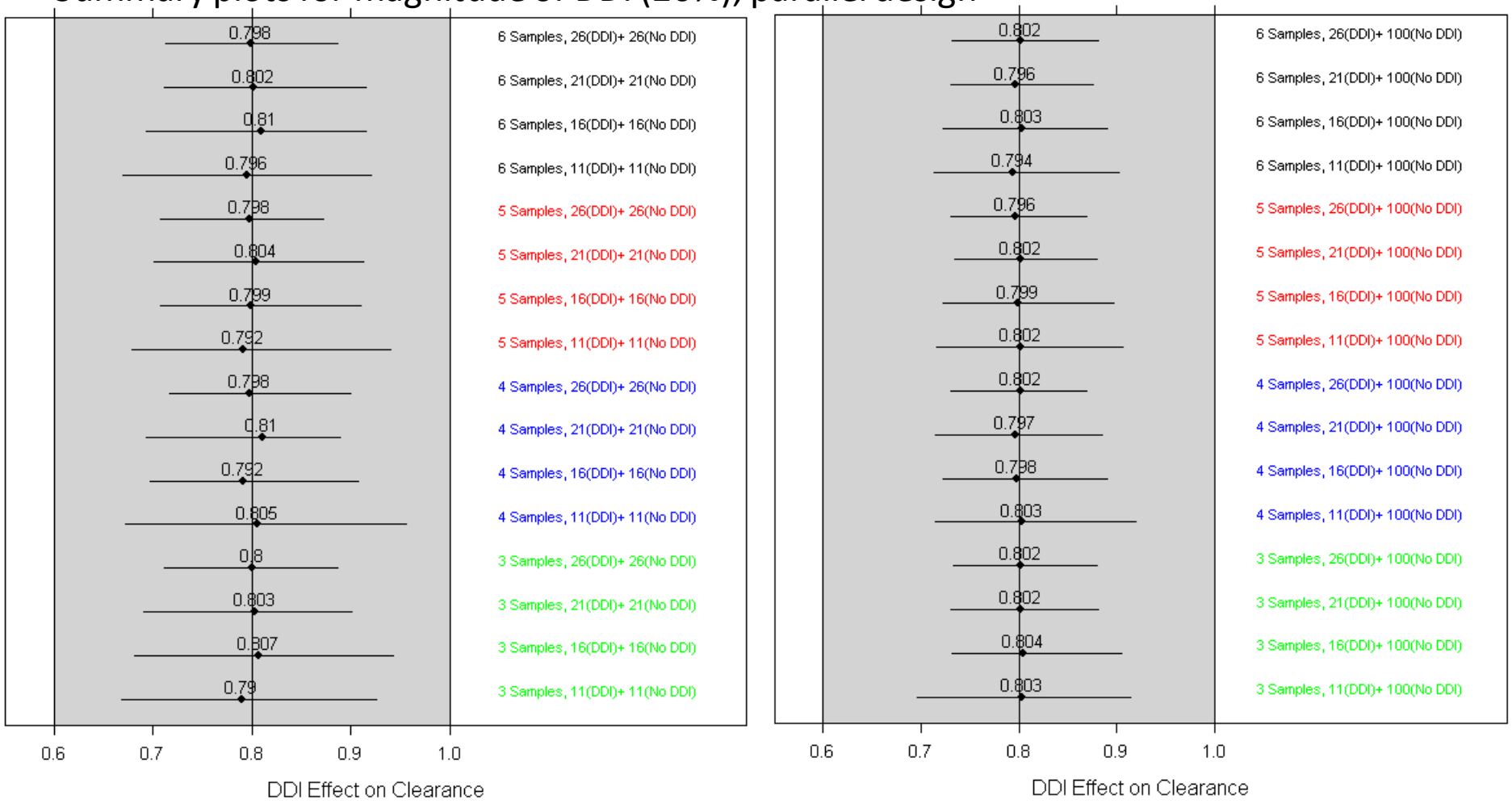
Summary plots for magnitude of DDI (0%), parallel design



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

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.

PopPK TP-DDI Taskforce

- Diane Wang, Ph.D.
- Chuanpu Hu, Ph.D.

Uppsala University

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

All grantees