Model-Informed and Model-Integrated Approaches in BE Assessment of Long Acting Injectable Products

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches

Topic 3: Emerging Use of Modeling and Simulation for Bioequivalence

Satish Sharan, PhD

Division of Quantitative Methods and Modeling, Office of Research and Standards

Office of Generic Drugs| CDER | U.S. FDA

September 30, 2020

Learning Objective

- Describe challenges in bioequivalence (BE) study for Long Acting Injectable Products

- Describe Model-Informed and Model-Integrated Approach for BE assessment of Long Acting Injectable Products

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.

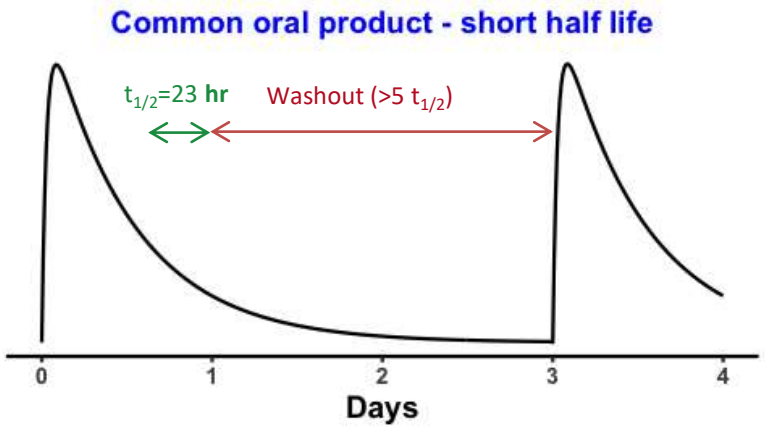
- These products can help improve patient compliance with a better therapeutic option to treat patients who adhere poorly to frequently administered medication.

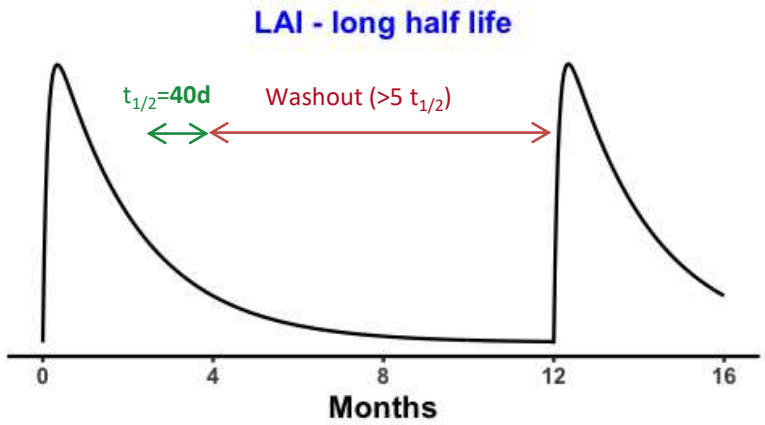
Examples of FDA Approved Long-Acting Injectable Drug Products

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)
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
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

Limited generic competition

Challenges in Bioequivalence Studies for Long-Acting Injectable Products - Long half-life ($t_{1/2}$)

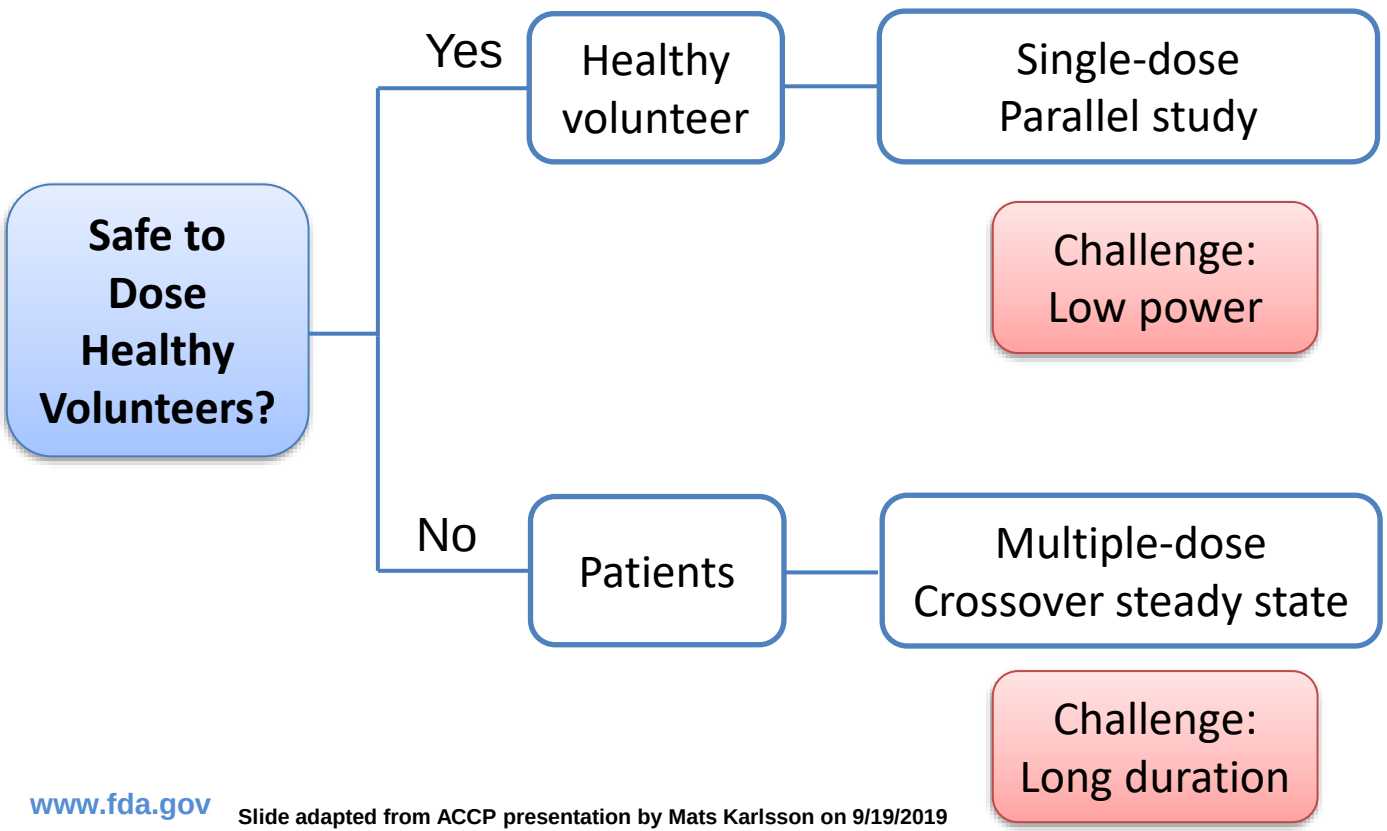




- Longer duration for BE studies
- High drop out rate
- Not practical to perform a single-dose crossover BE study

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

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

Model-Informed and Model-Integrated Approach

- **Model-Informed**
  - M&S is used to inform study designs, analysis methods
  - Aid in product development and help in 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

- Both approaches can help in reducing study durations and/or sample size, which can help in designing a more feasible BE study for LAI products.

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

M&S: Modeling & Simulation

Model – Informed Approach

GDUFA Research Initiative

Research Contract with Uppsala University (PI: Dr. Mats Karlsson; Contract #: 75F40119C10018) on Model Based Approaches to Improve BE Study Designs for LAI Products

Single-dose parallel study

Increase study power
(incorporating covariate effect)

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

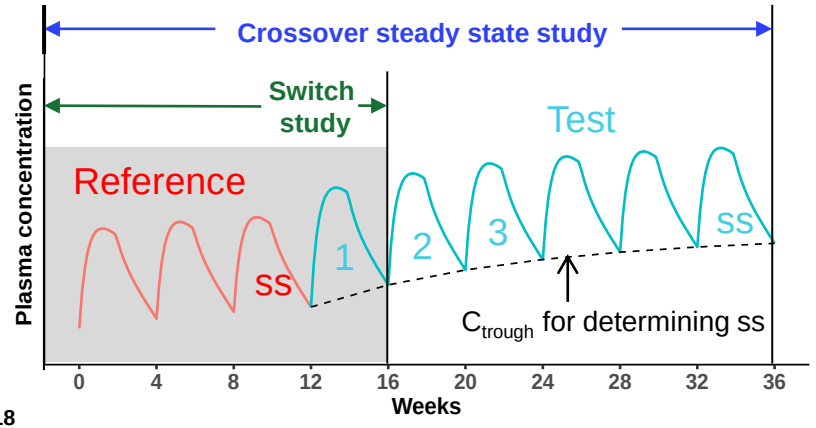
M&S

Multiple-dose crossover study

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

Reduce BE study duration

M&S



Example: Model-Informed Approach to Answer BE Study Design Question

- Aripiprazole is a LAI product approved for treatment of schizophrenia in adults and maintenance monotherapy treatment of bipolar I disorder in adults.

- Approved dosing regimen is to be administered monthly.

- Applicant proposed an alternate sampling design after the switch different than what is recommended in PSG.

PSG – Product-Specific Guidance

PSG for Aripiprazole Injectable Suspension (Dec 2014)

PSG for Aripiprazole recommends that in period 2 (when patients are switched from reference to test or vice versa), individual and mean blood drug concentration levels should also be reported during the first three dosing intervals. Intensive sampling should be performed during this period to accurately capture changes in trough and peak levels. This information will be used as supporting data for bioequivalence to confirm that any differences in Tlag does not result in significant transient differences in Cmin.

Active Ingredient: Aripiprazole

the products on established regimens.

As per 21 CFR § 314.94, the proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same to the reference product for both strengths (300 mg/vial and 400 mg/vial).

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

Bioequivalence based on (90% CI): Aripiprazole

In the evaluation of bioequivalence of the multiple dose study, the following pharmacokinetic data should be submitted for aripiprazole:

- Individual and mean plasma drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels (C_{min} ss)
- Individual and mean peak levels (C_{max} ss)
- Calculation of individual and mean steady-state $AUC_{interdose}$ ($AUC_{interdose}$ is AUC during a dosing interval at steady state)
- Individual and mean percent fluctuation [=100 * (C_{max} ss – C_{min} ss)/$C_{average}$ ss]
- Individual and median time to peak concentration

The log-transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and C_{max}) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product.

In period 2 (when patients are switched from reference to test or vice versa), individual and mean blood drug concentration levels should also be reported during the first three dosing intervals. Intensive sampling should be performed during this period to accurately capture changes in trough and peak levels. This information will be used as supporting data for bioequivalence to confirm that any differences in T_{lag} does not result in significant transient differences in C_{min}.

Waiver request of in vivo testing:
300 mg based on (i) acceptable bioequivalence studies on the 400 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Draft PSG Aripiprazole Intramuscular Extended Release Suspension (Dec/2014)

Model-Informed Approach to Aid BE Study Design and Sampling Strategy

- PopPK model used to simulate potential scenarios with Tlag differences for Test products and the impact of Tlag differences on PK during transition in cross-over study.
- Simulation shows intensive sampling during first dosing interval after the switch can be more informative to detect Tlag differences between RLD and TEST.
- Model-Informed approach can help applicants design and justify appropriate sampling strategy.

PopPK – Population Pharmacokinetics
RLD – Reference Listed Drug

Poll Question

Have you thought about leveraging innovative model informed/integrated approaches in your BE study?

A. Yes

B. No

Model-Integrated Approach

- **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

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

Model-Integrated BE Method Developed by Uppsala University

Model-Integrated Approach

Data

↓

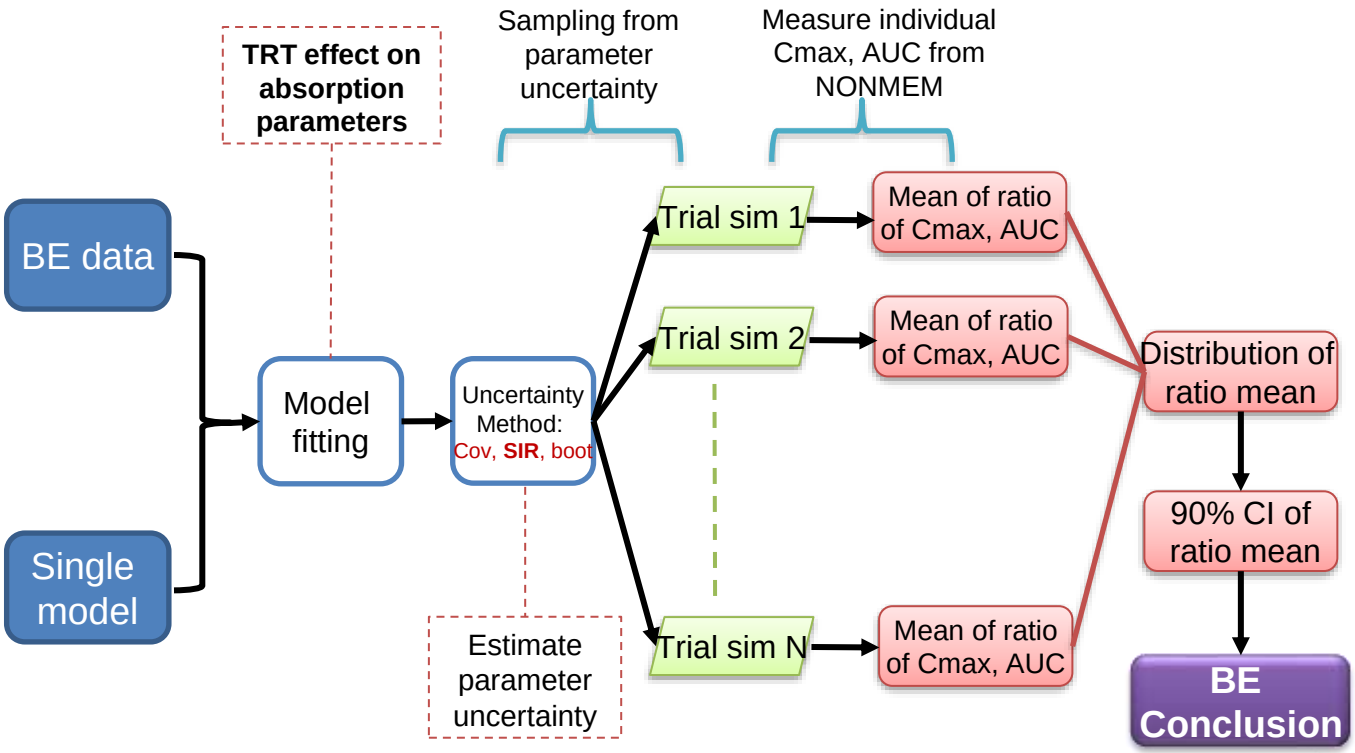
Modeling

↓

Simulation

↓

Conclusion



Mats Karlsson (Uppsala University), Contract #: 75F40119C10018

Regulatory Consideration for Application of Model-Integrated Approach for BE Analysis

- Virtual BE trial simulations should be performed in planning and designing the Model-Integrated Approach for BE Analysis.
- Simulations can be helpful in assessment of the performance of proposed modeling analysis plan (MAP).
- The MAP and study design should be pre-specified.
- In scenario where M&S will be used for pivotal decision making (BE conclusion), external validation (applicant can prespecify) can be useful in providing the confidence in the prediction performance of the model.

Regulatory Consideration for Model-Integrated Approach for BE Analysis

- Assessment of the parameter estimates uncertainty and their impact on the BE determination.
- Appropriate control of type 1 (from the agency) and type 2 errors.
- Due to the complexity of the analysis encourage early interaction with Agency.

Resources

- FDA draft guidance Population Pharmacokinetics Guidance for Industry (July 2019)
- FDA Guidance for Industry Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications (2003)
- FDA draft guidance Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry (Nov 2019)
- Leveraging Quantitative Methods in Reviewing Complex/Locally Acting Products (October 2-3, 2017)

Summary

- Development of Long-Acting Injectable Products is challenging.

- Model-Informed and Model-Integrated approach can save time and resources in development of Long-Acting Injectable Products.

- FDA welcome innovative alternative approaches to demonstrate bioequivalence.

Thank You!

- Alternative approaches to demonstrate bioequivalence: Applicants can submit their proposal through FDA's Pre-ANDA program.
  - Pre-ANDA Program Information
  - For questions about submitting Pre-ANDA meeting requests for complex generic drug products online please contact PreANDAHelp@fda.hhs.gov

Acknowledgement

OGD/ORS/DQMM

Liang Zhao
Lanyan (Lucy) Fang
Selim Fakhruddin
Quantitative Clinical Pharmacology (QCP) Team

OGD/ORS-IO

Robert Lionberger
Lei Zhang

External Collaborators

Uppsala University,
Contract # 75F40119C10018

Mats Karlsson, Ph.D.
Andrew Hooker, Ph.D.
Xiaomei Chen, Ph.D.
Piyanan Assawasuwannakit (Jill), Ph.D.

Challenge Question # 1

Q) What are the challenges in bioequivalence study of long-acting injectable products?

1) Long durations of bioequivalence studies
2) Highly variable gastric emptying time
3) Both 1 and 2
4) None of the above

Challenge Question # 2

Q) Model-Informed approach can be used to:

1) Design PK sampling strategy for BE study
2) Reduce BE study duration
3) Both 1 and 2
4) None of the above

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Satish Sharan, PhD

Division of Quantitative Methods and Modeling, Office of Research and Standards
Office of Generic Drugs| CDER | U.S. FDA

Closing Thought

FDA welcome innovative alternative approaches to demonstrate bioequivalence & Applicants can submit their proposal through FDA's Pre-ANDA program.


FDA
U.S. FOOD & DRUG
ADMINISTRATION