Model-Integrated Evidence for Bioequivalence Assessment of Long-Acting Injectables From a Generic Drug Perspective

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November 30, 2021

Disclaimer

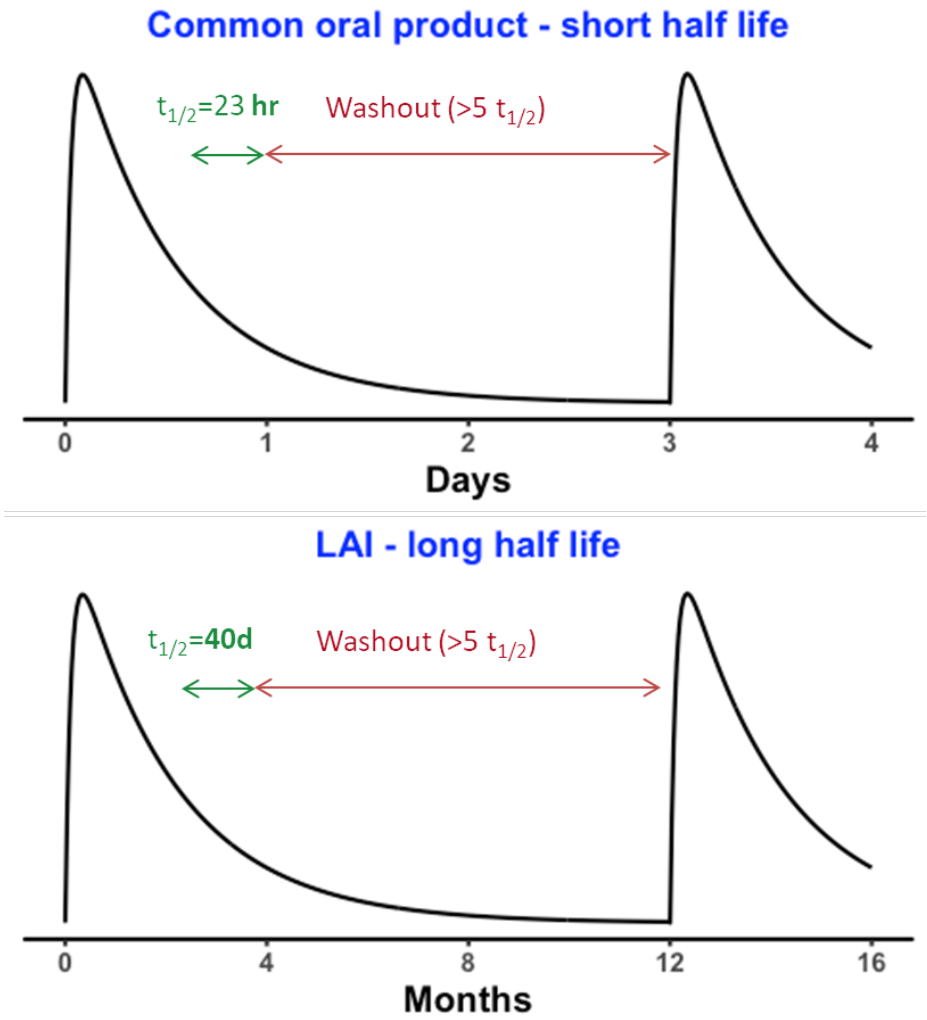
This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

- Challenges in Bioequivalence (BE) Studies for Generic Long-Acting Injectable and Implantable (LAIs) Drug Products
- Opportunities with Model-Integrated Approaches
- Regulatory Experience
- Current Gaps/Open Questions

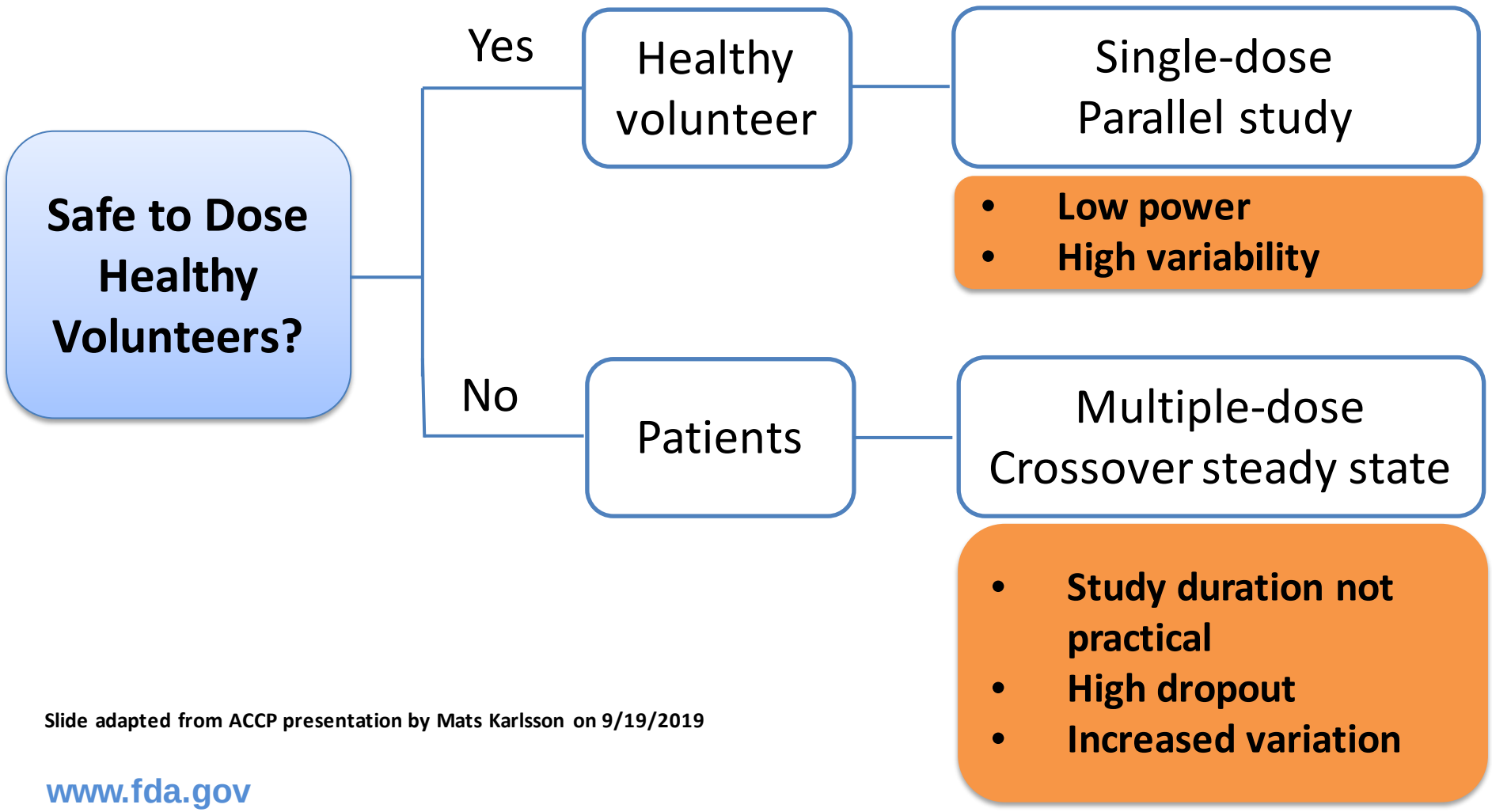
Challenges in BE Studies for Generic LAIs

- Extended-release formulations intended for reduced dosing frequency
- Challenges in BE include:
  - Long study duration
    - Long half-life due to slow release of drug from formulation, not elimination
  - High Pharmacokinetic (PK) variability/Large sample size
  - Steady state BE studies in patients
    - Attainment of steady state
    - Patient recruitment



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

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

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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

Opportunities with Model-Integrated Evidence BE Approach

- Model-integrated evidence (MIE) approach* uses models to generate pivotal evidence for BE decision
- MIE can support product approval via
  - a prespecified model-based analysis of an in vivo BE study
  - a virtual bioequivalence (VBE) study
- MIE can support alternative BE approach to otherwise recommended *in vivo* BE studies in combination with relevant *in vitro* BE tests
- This workshop focused on MIE with population PK modeling and simulation

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

MIE for LAIs with Mechanistic PBPK Modeling

- Mechanistic models can integrate key formulation attributes and physiology
  - Integrate key formulation attributes and physiology to predict bioavailability
    - Predict effects of particle size, surface morphology of Active Pharmaceutical Ingredient (API), pH and viscosity of formulation on systemic PK
    - Define safe space between test and reference drug products
  - Explain source of PK variability on a mechanistic basis
    - Based on the interaction of API with physiology such as interaction with local immune cells
    - Account in vivo aggregation of particles at injection depot after drug administration
  - Guide selection of clinically relevant/in vivo predictive in vitro studies
  - Mechanistic in vitro-in vivo correlation (IVIVC) by incorporating in vitro release or dissolution data in physiologically based PK (PBPK) models
- PBPK models can support product approval via in silico/virtual BE studies

Slide courtesy of Dr. Khondoker Alam (with modifications)

OGD Supports Model-Based BE for LAIs

- Generic Drug User Fee Amendments (GDUFA) Research
  - External research to support development of innovative MIE BE approaches for LAIs
  - Internal research to support assessment of applicant proposals on MIE BE for LAIs
- Model-Based BE for LAI Product-Specific Guidances
  - Paliperidone palmitate (recommended in Aug 2021)
  - Levonorgestrel Intrauterine Device (revised Jan 2020)

FDA Funded Grants/Contracts Modeling and Simulation 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
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

Pre-ANDA Meeting Experience – Examples

- Several innovative approaches using MIE submitted by Generic Drug Industry for LAI products.

- Examples of MIE purposes
  - Reduce study duration and/or sample size
  - Alternative BE metrics associated with narrowed BE limits
  - Less burdensome sampling scheme

- Examples of MIE strategies
  - Leveraging published population PK models
  - In vivo clinical PK studies that are different from recommended BE studies for model development/adjustment
  - In silico BE studies for BE demonstration
  - Virtual BE studies to justify the proposed study designs or other aspects for MIE

Regulatory Considerations for Using MIE

- Meeting regulatory standards to generate BE evidence
  - Sensitive to detect formulation difference with confidence
  - Reasonable passing rate for BE products
- Sufficient model verification and validation for the intended regulatory use
  - Capable to discern formulation difference with type 1 error control
  - Characterization of uncertainty and impact on BE determination
- 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)

Model-Integrated BE for LAIs – Current Progress and Gaps

- Advantages:
  - Have promises to address current challenges in LAI BE
    - Can use more feasible in vivo study designs (e.g., shorter duration)
    - Can handle comparing differences in rate and extent of absorption with controlled type 1 error between test and reference products
- Challenges:
  - Validation and verification of models/approaches for the purpose of MIE
  - Predefining models may be challenging
  - Analysis not as simple as conventional noncompartmental analysis (NCA) method

MIE Discussed at FY22 GDUFA Science and Research Initiatives Public Workshop

Sub Session 1B: Leveraging model integrated evidence for long-acting injectables (LAIs) to reduce regulatory barriers

- Use of model-integrated approach to reduce sample size and study duration for LAIs BE studies.
- Use of model-integrated approach to explore potential new and more sensitive data analysis method.
- Use of model-integrated approach to assess the time for LAIs to reach the steady sate and determine number of doses required in study protocol designs.
- Understanding of mechanistic aspects to establish a potential in vitro-in vivo correlation (IVIVC) of LAIs.

Slide courtesy of Dr. Yuqing Gong

GDUFA Science and Research Initiatives: Request for Public Input on FY 2022 Generic Drug Research, Virtual Public Workshop, June 23, 2021.

Summary

- Key challenges in applying MIE for LAI BE assessment
  - Clarity on the acceptable model validation and verification for MIE applications
    - MIE application scenarios can vary for difference cases requiring a different type/level of validation
  - Evolving BE approaches/methodologies
    - Utility and validity of the approaches are still being explored
- FDA and Center for Research on Complex Generics initiatives to develop and establish best practice in MIE for BE
  - Time to build consensus in MIE for BE
  - A public workshop to foster communication and collaborations with multiple stake holders

Acknowledgement

OGD/ORS/DQMM

Satish Sharan

Yuqing Gong

Quantitative Clinical Pharmacology (QCP) Team

Lanyan (Lucy) Fang

Liang Zhao

OGD/ORS/IO

Robert Lionberger

Lei Zhang

External Collaborators

Uppsala University,

Contract # 75F40119C10018