Model-Integrated Bioequivalence Establishment: Long-Acting Injectable Drug Products

GRx+Biosims 2021

Day 3 Science and Regulatory Learning Tracks: Innovation in Generic Drug Development and Assessment

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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.

Outline

- Challenges in Developing Generic Long-Acting Injectable (LAI) Drug Products
- Opportunities with Model-Integrated Approaches to Support Generic LAI Development and Assessment
- FDA Efforts to Support Innovative Bioequivalence (BE) Approaches of Model-Integrated BE for LAIs
- Summary

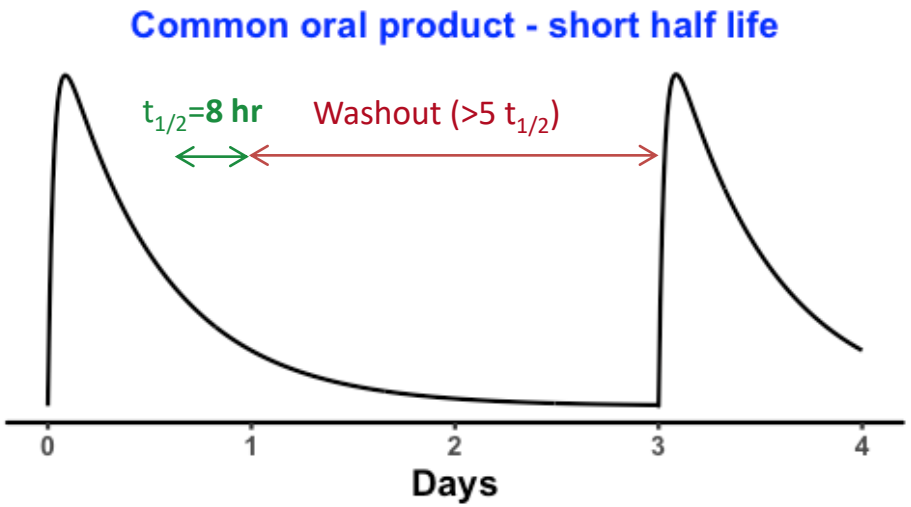
Long-Acting Injectable Drug Products

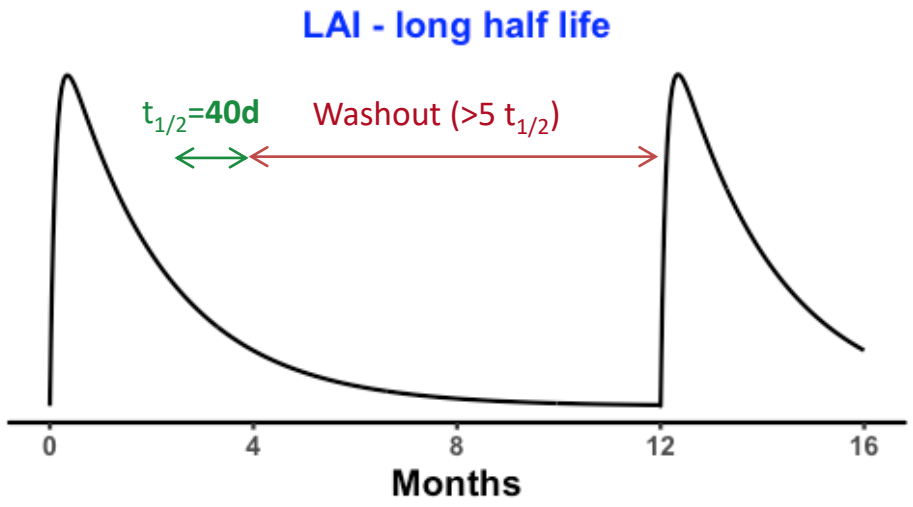
- Long-acting injectable (LAI) drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular, subcutaneous, intravitreal, or other routes.

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

Challenges of Performing BE Studies for LAI - Long half-life ($t_{1/2}$)

Single dose crossover BE study not practical or recommended

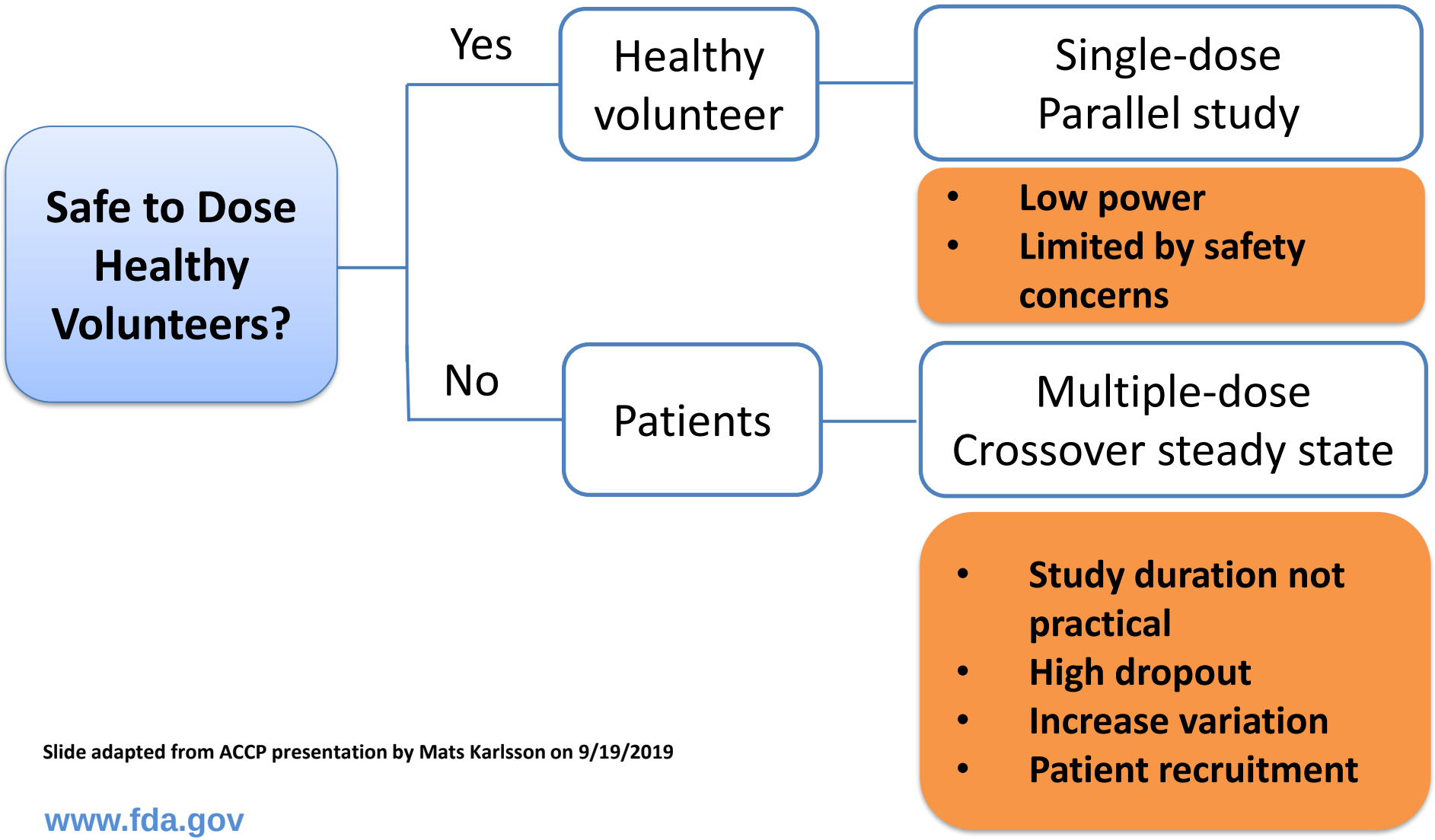




- **Long washout time**
- **Safety concerns**

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

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

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	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
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	8
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	1
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

Model-Integrated BE Approaches

- Model-based BE approach includes modeling and simulation in drug development and decision making

- Model-integrated evidence (MIE) approach* refers to using models such as virtual BE studies not just to plan a pivotal study but to serve as pivotal evidence for supporting
  - **product approval** via
    - a prespecified model-based analysis of an in vivo BE study
    - a virtual bioequivalence (VBE) study
  - **alternative** BE approach to otherwise recommended *in vivo* BE studies in combination with relevant *in vitro* BE tests

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

Opportunities with Model-Integrated BE for LAI Drug Products

Model-informed approach

To modify NCA-based BE methods for LAI

Model-integrated approach

To include modeling and simulation generated data in LAI BE evaluation

Reduce sample size and/or reduce study duration

Make LAI BE study more feasible

- **Novel/optimal study design**
- **Hybrid approach (e.g., partial/small size in vivo BE study data + virtual BE studies for conclusion)**
- **Alternative BE limits**

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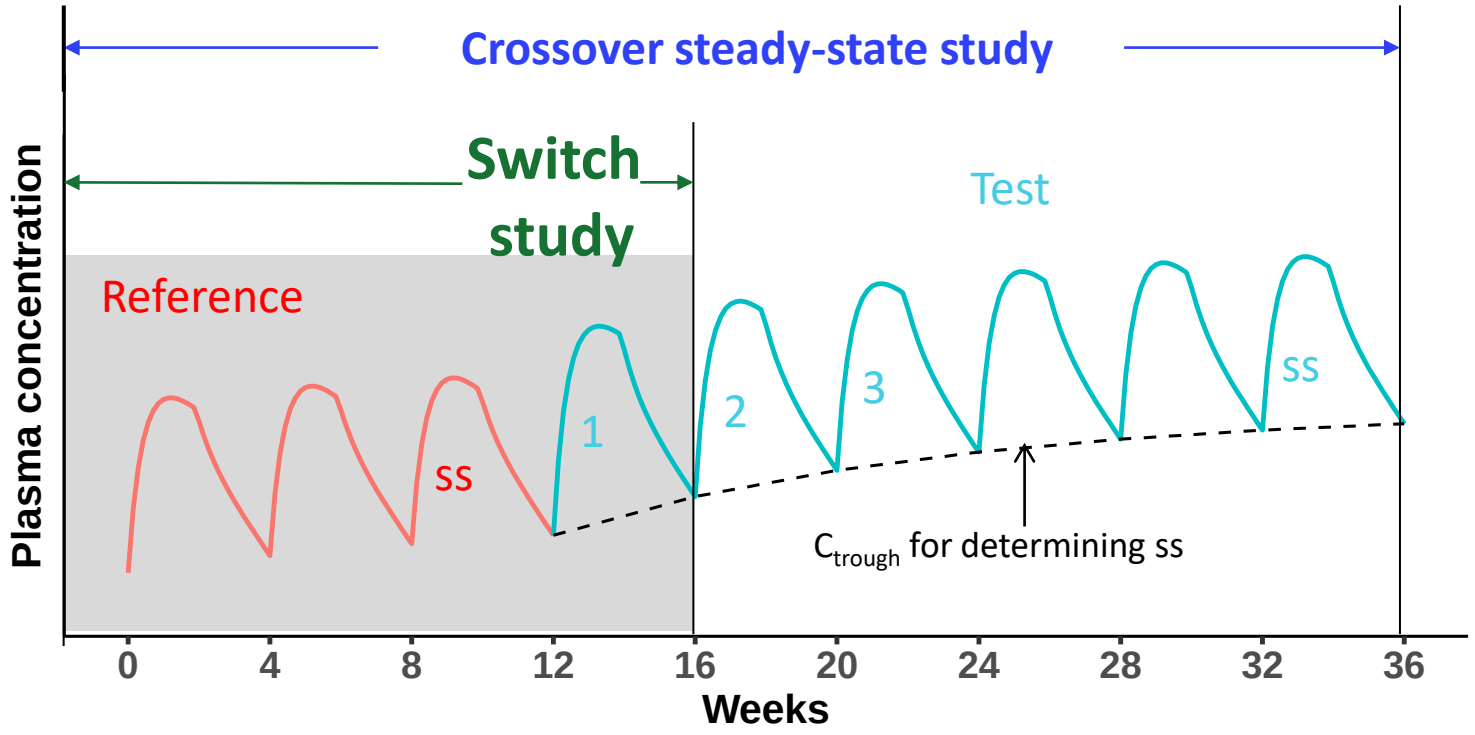
An Example of an Innovative Study Design for Model-Integrated BE for LAIs:

a switch study to reduce study duration



Model-integrated BE

The BE analysis includes Pharmacokinetic (PK) modeling

Data from BE study

↓

Pre-specified Model

↓

Simulation

Virtual BE study using a standard single dose crossover design

↓

Conclusion

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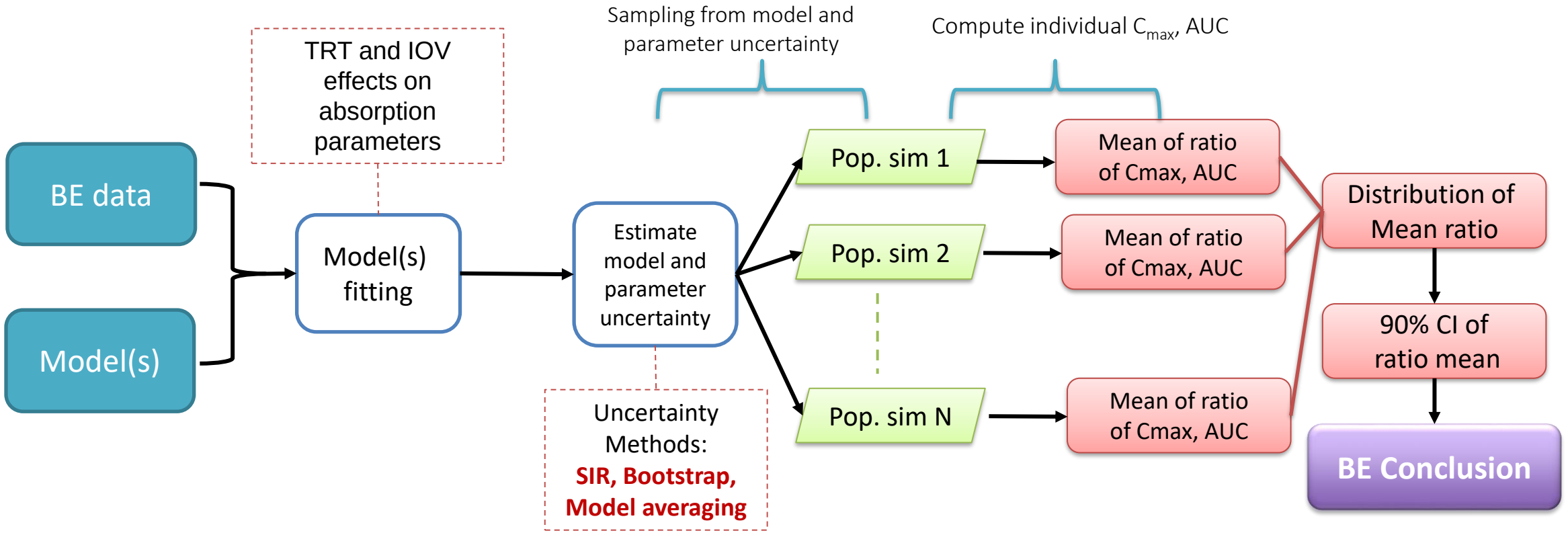
Model-Integrated BE Framework for LAI

The BE Analysis Includes PK Modeling



Modeling → **Uncertainty estimation** → **Simulation** → **Conclusion**

- ACOP 2019, Andrew Hooker, Development and comparison of model-based bioequivalence analysis methods on sparse data.
- ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.

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

Model-Integrated Approach – Research Findings

- Advantages:
  - Can reduce study duration than the currently recommended steady state crossover study design
  - Can handle comparing differences in rate and extent of absorption with controlled type 1 error
  - Can account for model structure and parameter uncertainty
- Challenges:
  - Predefining models may be challenging, but can be done
  - Analysis not as simple as conventional NCA method

Further Research is Warranted for Model-Integrated BE

- Other opportunities can be explored to help demonstrate the utility/validity of model-integrated evidence approach for generic LAI development and approvals
- Some potential opportunities include, but are not limited to:
  - Can the evaluation method be more-convenient and simple?
  - Can we allow fewer samples per subject?
  - Can we take a hybrid approach? For example,
    - Can we use actual observation for Cmax and modeling for AUC?
    - Can we use a partially conducted PK study to simulate steady state for BE analysis?
  - Can we make the study shorter using other novel study designs? For example,
    - Can we use non steady state data to do the assessment?
- Model-integrated BE strategies can be applied to other product categories with similar challenges in clinical BE studies

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
  - Characterization of uncertainty and impact on BE determination
  - Capable to discern formulation difference with type 1 error control
- 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)

Pre-ANDA Meeting Experience

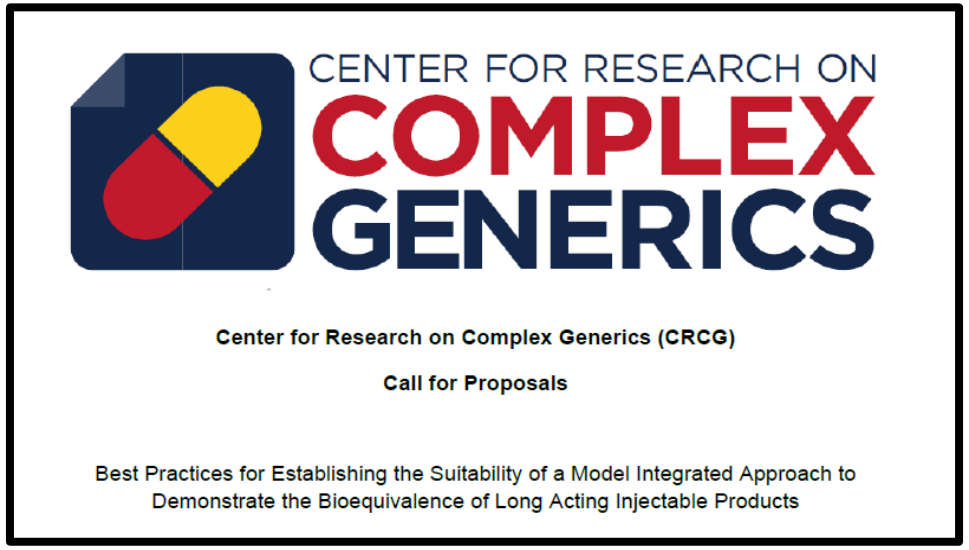
- Several innovative approaches using MIE submitted by Generic Drug Industry for LAI products.
- Due to the complexity of the analysis encourage early interaction with Agency
- Identified challenges in applying MIE for BE assessment
  - Consensus not clear for acceptable model validation and verification for MIE applications
  - MIE scenarios can vary for difference cases and may need a different type/level of validation
- Initiatives to develop and establish best practice in MIE
  - FDA-industry information exchange via pre-ANDA interactions
  - Public workshop for multiple stake holder communications/collaborations

A Public Workshop to Foster Open Forum Discussion on Best Practice for MIE for LAI BE

Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products

The workshop will be held on November 30, 2021 in collaboration with Center for Research on Complex Generics (CRCG)
http://www.complexgenerics.org/

FDA-CRCG to Support Open Forum Discussion on Best Practice Development



CRCG Call for Proposals Results

Congratulations to **Géraldine Ayral, Joel Owen and Clémence Pinaud at SimulationsPlus** (Lixoft and Cognigen divisions), and **Joga Gobburu at the University of Maryland School of Pharmacy** for initiating CRCG research projects on "Best Practices for Establishing the Suitability of a Model Integrated Approach to Demonstrate the Bioequivalence of Long Acting Injectable Products."

- The awardees will present in the FDA-CRCG workshop
- The study outcomes are planned to be published in scientific journals

Example Topics for Best Practice Discussion in MIE for LAI BE

- To extrapolate sufficiently verified and validated models from Reference Listed Drug (RLD) holders to design in vivo studies for BE demonstration
- To use the results from a partially conducted in vivo steady state study (e.g., 2-3 dose administration only) and simulate recommended steady state PK data for BE analysis
- To use models built on a small sample size (not adequately powered to demonstrate BE) to conduct virtual BE studies (that provides adequate statistical power for BE) for BE analysis
- To communicate expectations on the pre-specified modeling analysis plan (MAP) that corresponds to the proposed model-integrated BE study design
- To determine which part of the MAP should be pre-specified, and where post-hoc analysis can and/or should be allowed

Summary

- Development of Long-Acting Injectable Products is often challenging.
- Model-Integrated Evidence approach provides opportunity to save time and resources in development of Long-Acting Injectable Products.
- FDA supports innovative alternative approaches to demonstrate bioequivalence to overcome challenges in generic drug development and assessment.
- It is time to build consensus in Model-integrated Evidence for BE and a public workshop will be held to help develop best practices in Model-Integrated BE for Long-Acting Injectable and Implantable Drug Products.

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)

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