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

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Liang Zhao, Ph.D.
Division of Quantitative Methods and Modeling, Office of Research and Standards,
Office of Generic Drugs | CDER | U.S. FDA
Disclaimer

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

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, 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.
<table>
<thead>
<tr>
<th>Trade Names</th>
<th>Ingredient</th>
<th>Indication</th>
<th>Dose Frequency</th>
<th>Approved Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABILIFY MAINTENA KIT</td>
<td>ARIPIPRAZOLE</td>
<td>Schizophrenia; bipolar I disorder</td>
<td>Monthly</td>
<td>0</td>
</tr>
<tr>
<td>ARISTADA</td>
<td>ARIPIPRAZOLE LAUROXIL</td>
<td>Schizophrenia</td>
<td>Monthly</td>
<td>0</td>
</tr>
<tr>
<td>ARISTADA INITIO KIT</td>
<td>ARIPIPRAZOLE LAUROXIL</td>
<td>Schizophrenia</td>
<td>One time</td>
<td>0</td>
</tr>
<tr>
<td>SUBLOCADE</td>
<td>BUPRENORPHINE</td>
<td>Opioid use disorder</td>
<td>Monthly</td>
<td>0</td>
</tr>
<tr>
<td>PROBUPHINE</td>
<td>BUPRENORPHINE HYDROCHLORIDE</td>
<td>Opioid Dependence</td>
<td>one time (6 months)</td>
<td>0</td>
</tr>
<tr>
<td>CABENUVA KIT</td>
<td>CABOTEGRAVIR; RILPIVIRINE</td>
<td>HIV-1 treatment</td>
<td>Monthly</td>
<td>0</td>
</tr>
<tr>
<td>ATRIDOX</td>
<td>DOXYCYCLINE HYCLATE</td>
<td>Chronic adult periodontitis</td>
<td>1 week</td>
<td>0</td>
</tr>
<tr>
<td>BYDUREON BCISE</td>
<td>EXENATIDE</td>
<td>Improve glycemic control in type II diabetes</td>
<td>Weekly</td>
<td>0</td>
</tr>
<tr>
<td>BYDUREON .. BYDUREON PEN</td>
<td>EXENATIDE SYNTHETIC</td>
<td>Improve glycemic control in type II diabetes</td>
<td>Weekly</td>
<td>0</td>
</tr>
<tr>
<td>YUTIQ</td>
<td>FLUCINOLONE ACETONIDE</td>
<td>Chronic non-infectious uveitis affecting the posterior segment of the eye</td>
<td>36 months (one time)</td>
<td>0</td>
</tr>
<tr>
<td>ZOLADEX</td>
<td>GOSERELIN ACETATE</td>
<td>carcinoma of prostate, endometriosis, breast cancer</td>
<td>Monthly (4 weeks)</td>
<td>0</td>
</tr>
<tr>
<td>SUSTOL</td>
<td>GRANSETRON</td>
<td>Antiemetics for prevention of acute and delayed nausea and vomiting with chemotherapy</td>
<td>Weekly</td>
<td>0</td>
</tr>
<tr>
<td>LUPRON DEPOT... LUPRON DEPOT-PED</td>
<td>LEUPROLIDE ACETATE</td>
<td>Endometriosis, Fibroids, Advanced prostate cancer; children with central precocious puberty</td>
<td>1,3,4,6 months</td>
<td>0</td>
</tr>
<tr>
<td>ELIGARD</td>
<td>LEUPROLIDE ACETATE</td>
<td>Palliative treatment of advanced prostate cancer</td>
<td>1,3,4,6 months</td>
<td>0</td>
</tr>
<tr>
<td>DEPO-PROVERA</td>
<td>MEDROXYPROGESTERONE ACETATE</td>
<td>Prevention of Pregnancy</td>
<td>3 months</td>
<td>1</td>
</tr>
<tr>
<td>DEPO-SUBQ PROVERA 104</td>
<td>MEDROXYPROGESTERONE ACETATE</td>
<td>Prevention of pregnancy, endometriosis-associated pain</td>
<td>3 months</td>
<td>0</td>
</tr>
<tr>
<td>SINUVA</td>
<td>MOMETASONE FUROATE</td>
<td>Nasal polyps who had ethmoid surgery</td>
<td>3 months (one time)</td>
<td>0</td>
</tr>
<tr>
<td>VIVITROL</td>
<td>NALTREXONE</td>
<td>Alcohol/Opioid Dependence</td>
<td>Monthly (4 weeks)</td>
<td>0</td>
</tr>
<tr>
<td>SANDOSTATIN LAR</td>
<td>OCTREOTIDE ACETATE</td>
<td>Acromegaly, Carcinoid Tumors and Vasoactive Intestinal Peptide secreting tumors</td>
<td>Monthly (4 weeks)</td>
<td>0</td>
</tr>
<tr>
<td>ZYPREXA RELPREVV</td>
<td>OLANZAPINE PAMOATE</td>
<td>Schizophrenia</td>
<td>2, 4 weeks</td>
<td>0</td>
</tr>
<tr>
<td>INVEGA SUSTENNA</td>
<td>PALIPERIDONE PALMITATE</td>
<td>Schizophrenia, schizoaffective disorder, mood stabilizers or antidepressants</td>
<td>Monthly</td>
<td>0</td>
</tr>
<tr>
<td>INVEGA TRINZA</td>
<td>PALIPERIDONE PALMITATE</td>
<td>Schizophrenia</td>
<td>3 months</td>
<td>0</td>
</tr>
<tr>
<td>SIGNIFOR LAR KIT</td>
<td>PASIRETIDE PAMOATE</td>
<td>Acromegaly, Cushing’s Disease</td>
<td>4 weeks</td>
<td>0</td>
</tr>
<tr>
<td>PERSERI KIT</td>
<td>RISPERIDONE</td>
<td>Schizophrenia</td>
<td>Monthly</td>
<td>0</td>
</tr>
<tr>
<td>RISPERDAL CONSTA</td>
<td>RISPERIDONE</td>
<td>Schizophrenia, Bipolar I Disorder</td>
<td>2 weeks</td>
<td>0</td>
</tr>
<tr>
<td>XYOSTED (AUTOINJECTOR)</td>
<td>TESTOSTERONE ENANTHATE</td>
<td>Testosterone replacement therapy</td>
<td>weekly</td>
<td>0</td>
</tr>
<tr>
<td>ZILRETTRA</td>
<td>TRIAMCINOLONE ACETONIDE</td>
<td>Osteoarthritis pain of the knee</td>
<td>3 months (one time)</td>
<td>0</td>
</tr>
<tr>
<td>TRIPOTUR KIT</td>
<td>TRIPOTURELIN PAMOATE</td>
<td>precocious puberty</td>
<td>24 weeks</td>
<td>0</td>
</tr>
<tr>
<td>TRELSTAR</td>
<td>TRIPOTURELIN PAMOATE</td>
<td>Advanced prostate cancer</td>
<td>4/12/24 weeks</td>
<td>0</td>
</tr>
</tbody>
</table>
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

Approved for the treatment of schizophrenia or schizoaffective disorder

Paliperidone (Invega) NDA-21999

Extended release (ER) tablets with daily dosing (2006)

ER suspension injectable

NDA-22264; Invega Sustenna; every month - 2009
NDA-207946; Invega Trinza; every 3 month - 2015

www.fda.gov
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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initiation Dosing (deltoid)</th>
<th>Monthly Maintenance Dose (deltoid or gluteal)</th>
<th>Maximum Monthly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Day 1: 234 mg (150 mg eq.)</td>
<td>Day 8: 156 mg (100 mg eq.)</td>
<td>39 (25 mg eq.) - 234 mg (150 mg eq.)</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>234 mg (150 mg eq.)</td>
<td>156 mg (100 mg eq.)</td>
<td>78 mg (50 mg eq.) - 234 mg (150 mg eq.)</td>
</tr>
</tbody>
</table>
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.
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
Types of BE Study Designs for LAI Products

Safe to Dose Healthy Volunteers?

Yes
- Healthy volunteer
  - Single-dose Parallel study
  - Challenge: Low power

No
- Patients
  - Multiple-dose Crossover steady state
  - Challenge: Long duration

Safe to Dose

- Yes
- No

- 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

www.fda.gov
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

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

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

**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**

The BE analysis includes PK modeling

- Inform novel BE criteria

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

\[
\log(AUC)_i = \mu + \text{formulation} + \text{other covariates} + \epsilon_i
\]
Proposed Model-based BE Method Application
by Mats Karlsson

BE data and prior information

Model fitting

Uncertainty Method: Cov, SIR, boot

Estimate parameter uncertainty

Sampling from parameter uncertainty

Measure individual Cmax, AUC from NONMEM

Study sim 1
Mean of ratio of Cmax, AUC

Study sim 2
Mean of ratio of Cmax, AUC

Study sim N
Mean of ratio of Cmax, AUC

Distribution of ratio mean

90% CI of ratio mean

BE Conclusion

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)
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

<table>
<thead>
<tr>
<th>Project title</th>
<th>Study duration</th>
<th>Grantee/Contractor</th>
<th>Grant/Contract No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of model-informed bioequivalence evaluation strategies for long-acting injectable products</td>
<td>2019-2021</td>
<td>Uppsala University</td>
<td>75F40119C10018</td>
</tr>
<tr>
<td>Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection</td>
<td>2015-2019</td>
<td>University of Utah</td>
<td>U01FD005442</td>
</tr>
<tr>
<td>Development of PBPK simulation for long-acting injectable microspheres</td>
<td>2015-2018</td>
<td>Simulations Plus Inc.</td>
<td>U01FD005463</td>
</tr>
</tbody>
</table>

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](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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• Andrew Hooker, Ph.D.

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Simulations Plus, Inc., Grant #: U01FD005463
University of Utah Grant # U01FD005442
www.fda.gov/GDUFARegScience
Population PK Based Approaches to Evaluation Drug-Drug Interaction (1)

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

Summary plots for magnitude of DDI (0%), parallel design
Population PK Based Approaches to Evaluation Drug-Drug Interaction (2)

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

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