U.S. FOOD & DRUG ADMINISTRATION

Model-informed Drug Development for Long-acting Injectable Products

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September 16, 2019

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Outline

- **Overview**
- **Model informed drug development (MIDD)**
  - Approved regimen not studied in phase 3
  - Strategy to handle real life scenarios
- **Model integrated evidence for generic drug development and assessment**
  - Quantitatively evaluate the study design and sensitivity
  - Model informed Bioequivalence (BE) assessment
- **Take home messages**

Long Acting Injectables (LAI)

- Extended release injectable suspensions
  - Depot, slow release of the drug into systemic circulation
  - Decrease dosing frequency (every two weeks to three months)
- Unique Pharmacokinetic (PK) profiles:
  - an initial release phase: APIs on the surface of the formulation
  - a lag phase with minimal API release
  - a main release phase: ingredients in the formulation degrade allowing the API to be absorbed systemically
- Flip-flop kinetics: the apparent half-life is long (e.g., a few weeks) and determined by the slow release, rather than the rate of elimination

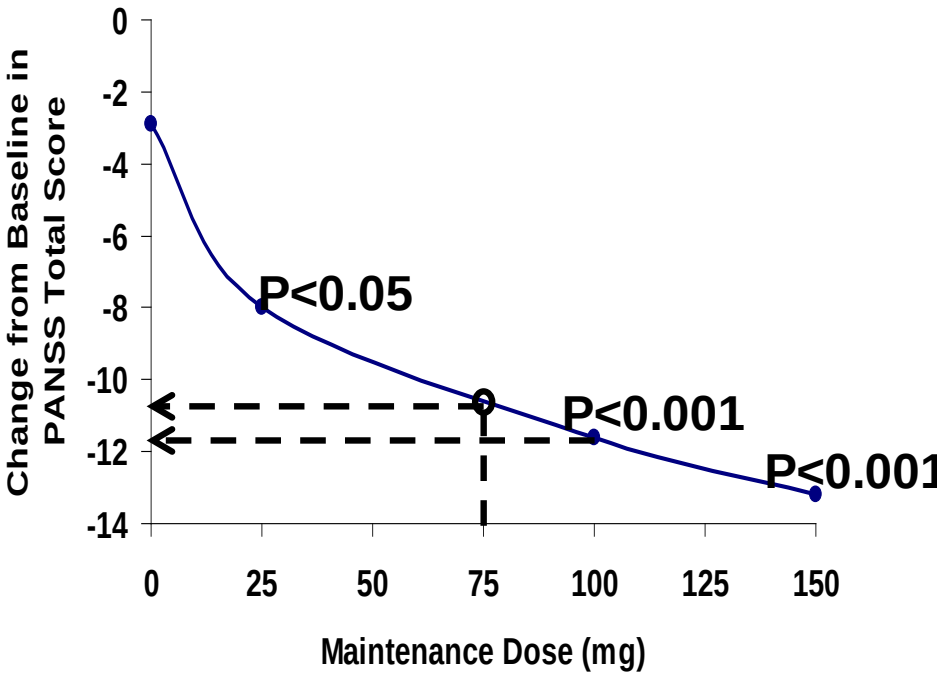
API: Active Pharmaceutical Ingredient

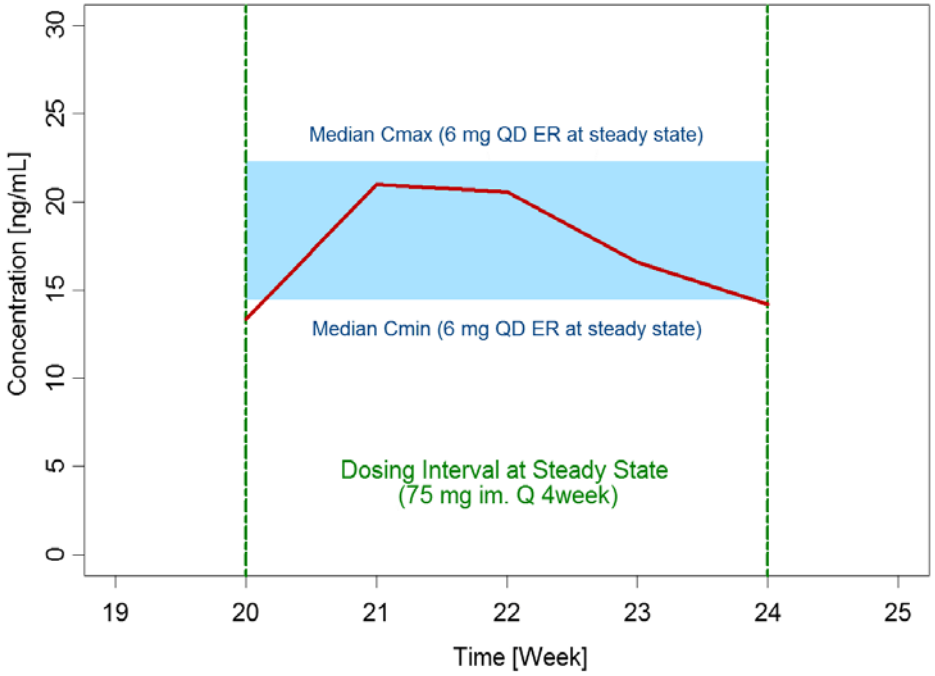
MIDD: Paliperidone Case

- **Indication: schizophrenia**
- **Extended-Release tablet is already approved (QD regimen)**
- **New monthly long acting injection formulation**
- **Regimens studied in phase 3 trials:**
  - **25 mg, 50 mg, 100 mg, 150 mg (day 1, 8, 36, 64)**
  - **150 mg (day1)+**
    - **25 mg (days 8, 36, and 64)**
    - **100 mg (days 8, 36, and 64)**
    - **150 mg (days 8, 36, and 64)**
- **Proposed regimen:**
  - **150 mg (day1), 100 mg (day 8) and 75 mg (monthly)**

Courtesy slide from Yaning Wang, Ph.D.

Selection of Unstudied Regimen



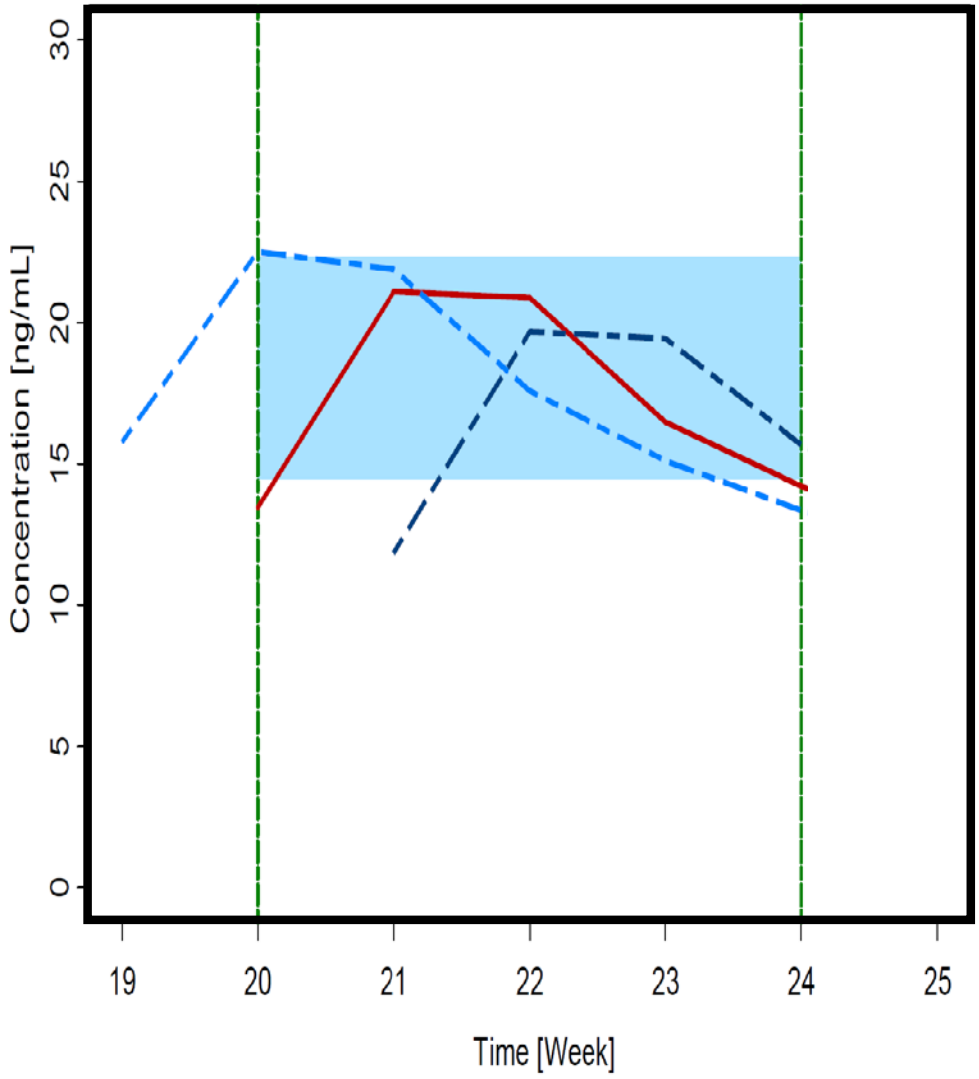


- N≅160/arm
- All active arms better than placebo
- Safety: one death at 150 mg and dose-dependent increase in body weight and serum prolactin levels

- Predicted steady state (SS) concentrations under 75 mg monthly regimen are within the blue region of 6 mg QD regimen, but 100 mg monthly regimen would be over this range.

PK Simulation for Dosing Window

- Dosing window
  - the 2nd dose
  - the monthly maintenance dose
- What to do after missing a dose?
- Switching from ER tablet or other antipsychotics
- Dosing regimen for patients with renal impairment



Model Informed Drug Development

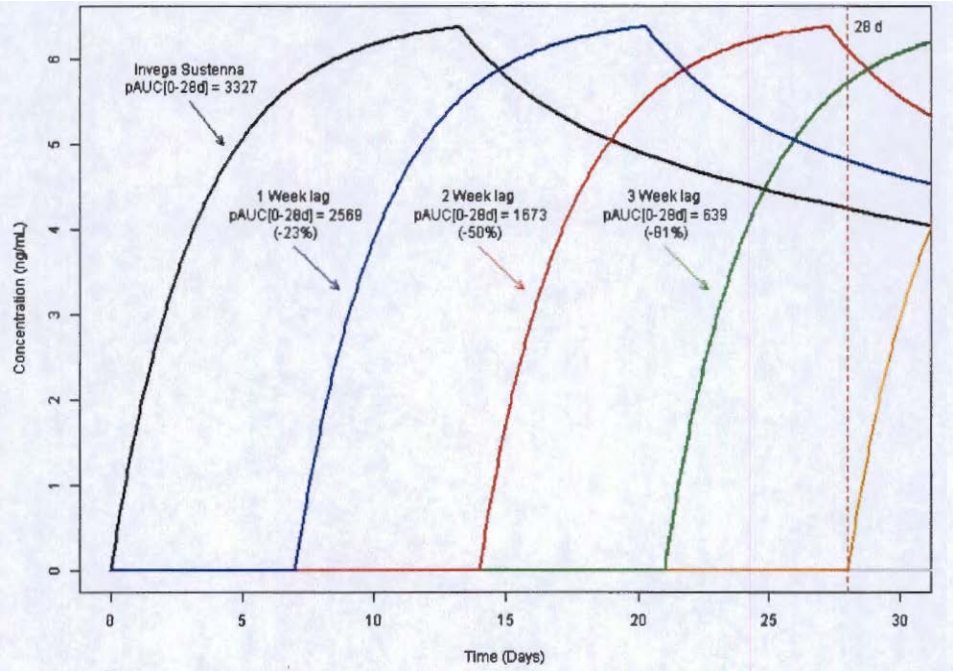
- Modeling & Simulation results support the approval of unstudied regimen
- PK simulations are used to address real-world practice challenges: dosing window, missing dose, switching from prior treatments, dosing regimen for special patients
- All these model based recommendations are included in the product labeling

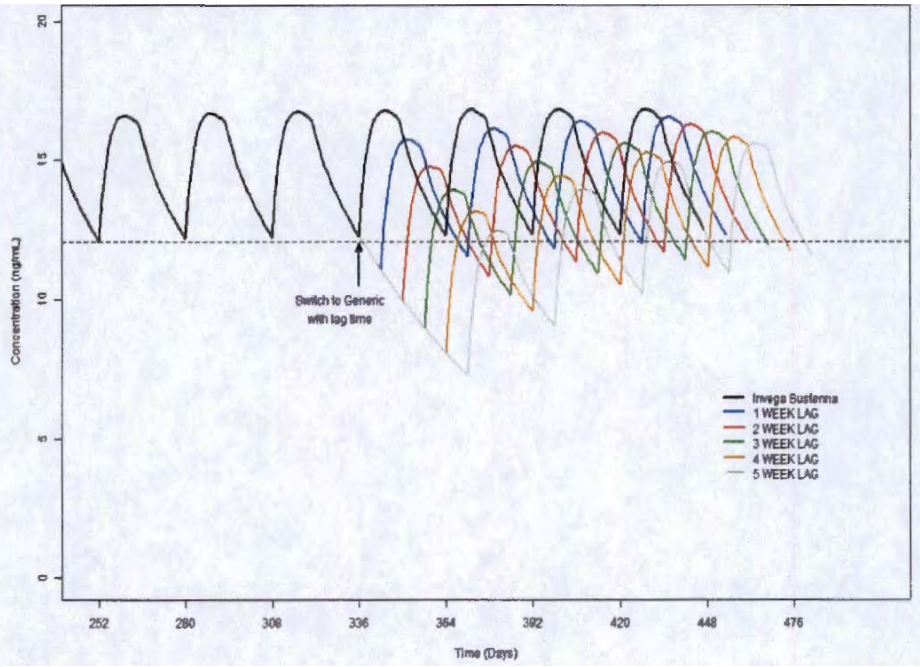
Courtesy slide from Yaning Wang, Ph.D.

Generic LAI Development

- Bioequivalence (BE) studies are challenging
  - Long study duration due to long half-lives
  - Large number of subjects due to high PK variability
  - Product-specific guidance (PSG) generally recommends **steady state** (SS) BE studies in patients due to safety concerns
- BE assessment needs special considerations
  - PSG generally have specific wording on individual steady state attainment
  - Conventional BE assessment methodologies necessitate long BE studies
  - When is the most sensitive time to detect product differences?
  - Alternative BE assessment approaches are encouraged

Release Differences are More Evident Immediately after Switching for Test Products with Delayed Release



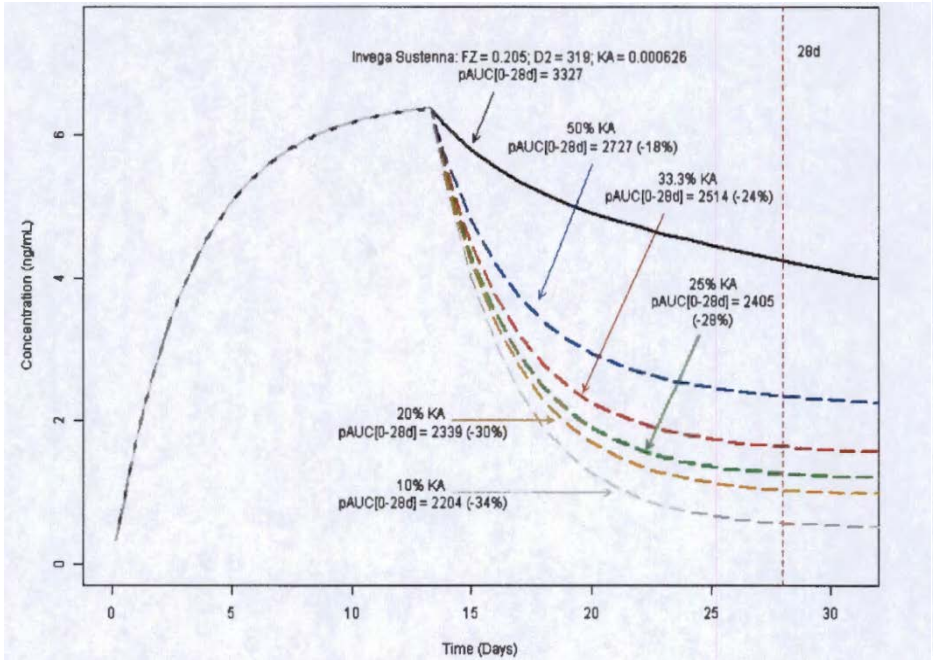


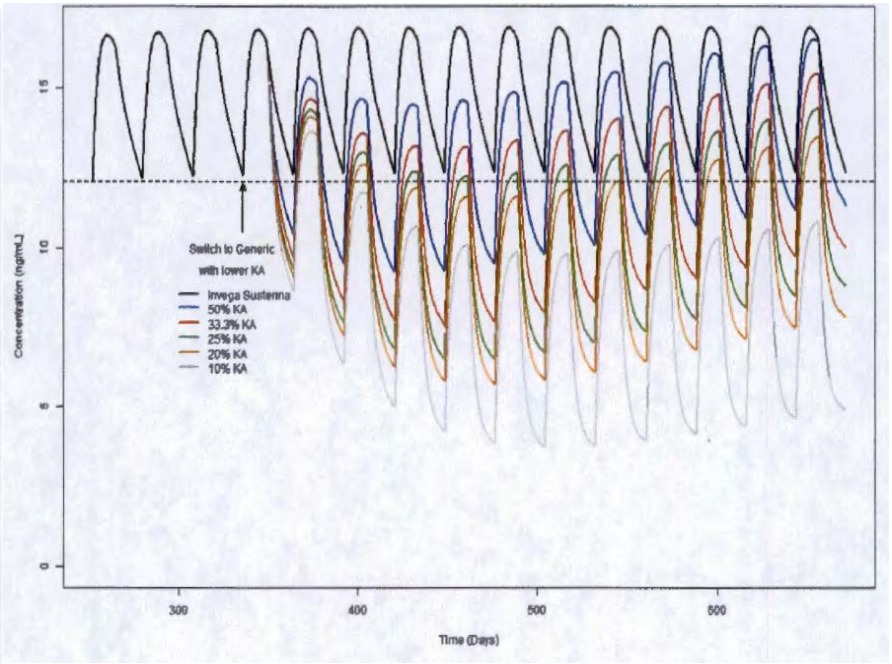
- Conventional BE metrics (Cmax and AUC) cannot differentiate these products with delayed release in SD PK studies
- pAUCs (such as $AUC_{0\text{-}28d}$) can differentiate PK profiles

- It will take a few months to reach new steady state after switching to products with delayed release
- Products with delayed release will have greater PK differences during the transition period after switch

Figures 3 and 10 in Citizen Petition FDA-2013-P-0608

Release Differences are More Evident after Attainment of SS for Test Products with Altered Release Rate





- Conventional BE metrics (Cmax and AUC) cannot differentiate these products with slower release rate in SD PK studies
- pAUCs (such as $AUC_{14\text{-}28d}$) can differentiate PK profiles

- It will take a few months to reach new steady state after switch to products with slower release rate
- Products with slower release rate will have greater PK differences at new steady state after switch

Figures 4 and 11 in Citizen Petition FDA-2013-P-0608

Pharmacometric Approaches

How Can Pharmacometric Approaches be Leveraged in Generic LAI Product Development?

- Designing adequately powered PK BE studies
  - Trial simulations comparing alternative designs
  - Optimal BE study design

- Model-based BE assessment
  - PK models fitted to the observed data
  - Account for residual drug exposure from prior treatment
  - Account for covariate effect on BE assessment
  - Steady state simulations
  - Enable BE assessment right after switch instead of at steady state

Take Home Messages

- Modeling and simulation approaches have been used throughout the lifecycle of long-acting Injectable products: drug development, regulatory approval, and dosing management in real-world clinical practice
- The model-based BE approaches are essential for complex LAI products, if ANDA applicants want to conduct BE studies in an efficient way
  - Quantitatively evaluate the study design and sensitivity
  - Maximize the information gained from efficient BE studies
  - Model-based BE assessment

ANDA: Abbreviate New Drug Application

Acknowledgements

- Division of Quantitative Methods and Modeling, Office of Research and Standards (ORS)
  - Sharan Satish, Ph.D.
  - Zhichuan (Matt) Li, Ph.D.
  - Hezhen Wang, Ph.D.
  - MJ Kim, Ph.D.
  - Liang Zhao, Ph.D.
- Office of Research and Standards (ORS)
  - Lei Zhang, Ph.D.
  - Robert Lionberger, Ph.D.
- Office of Bioequivalence (OB)
  - Bing Li, Ph.D.
  - Ethan Stier, Ph.D.
  - Nilufer Tampal, Ph.D.
- Office of Clinical Pharmacology (OCP)
  - Yaning Wang, Ph.D.
  - Hao Zhu, Ph.D.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