PK and Statistical Considerations for Steady State Bioequivalence Studies - FDA Perspective

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- Disclaimer

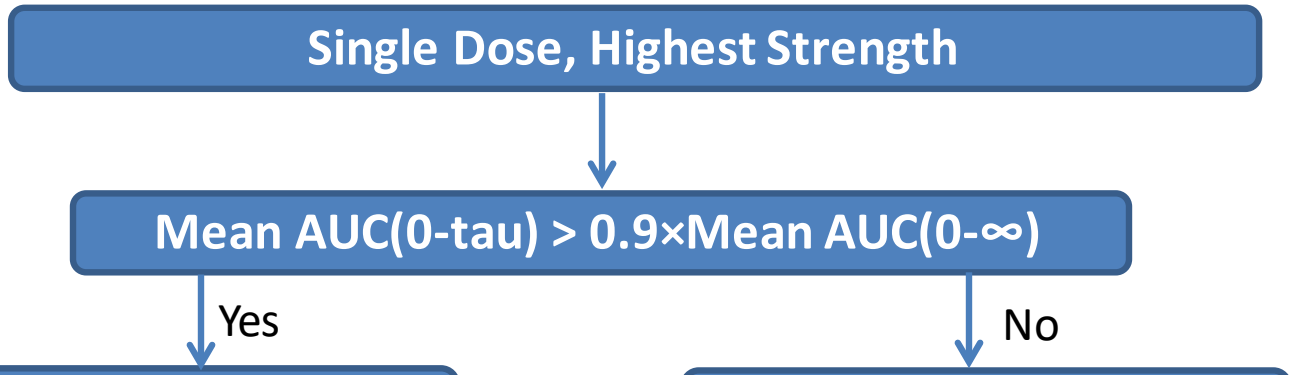
Outline

- Overview of Regulatory Guidelines
  - Bioequivalence for modified release products (EMA&USFDA)
  - FDA general guidance for industry
  - Product specific guidance (PSG)

- Paliperidone (INVEGA SUSTENNA®): A Case Study
  - Study design
  - Steady state attainment
  - BE analysis

- Take home messages

EMA Guidance for Modified Release (MR) Products



	Single Dose Fasting Study	Single Dose Fed Study	Multiple Dose Study
Cmax	Yes	Yes	No
AUC(0-t)	Yes	Yes	No
AUC(0-∞)	Yes	Yes	No
partialAUCs	Yes	Yes	No
Cmax, ss	No	No	No
Cτ, ss	No	No	No
AUC(0-τ)ss	No	No	No

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AUC(0-τ)ss	No	No	Yes

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms. (EMA, 20th November 2014)

USFDA Guidance for Oral MR Products

3. Bioequivalence Studies

For modified release products, we recommend the following studies: (1) a single-dose, fasting study comparing the highest strength of the test with the RLD, and (2) a single-dose fed BE study comparing the highest strength of the test with the RLD product. Because single-dose studies are considered more sensitive in addressing the primary question of BE (e.g., release of the drug substance from the drug product into the systemic circulation), multiple-dose studies are generally not recommended.

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Guidance for Industry; Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Draft Guidance)

FDA's Perspective on Oral MR Products

- A steady state BE study is generally not recommended for oral extended-release (ER) products which tend to accumulate after multiple dosing at the recommended dosing interval, but additional metrics/criteria may apply for single dose study.
  - Partial AUC (pAUC): amphetamine ER products
  - Tmax: naproxen ER products
  - Tlag: lamotrigine ER products
- FDA has conducted extensive research to ensure BE established based on single dose studies are relevant to chronic dosing for MR products.
  - Bioequivalence Standards for Narrow Therapeutic Index (NTI) Drugs: Are They Stringent Enough to Ensure Safety and Efficacy? L Fang, ASCPT meeting, 2015

When to Conduct Steady State BE Studies?

- When safety considerations suggest using patients who are already receiving a medication, often the only approach to establish BE without disrupting a patient's ongoing treatment is in a steady-state study. If a steady-state study is used, we recommend that applicants carry out **appropriate dosage administration and sampling to document the attainment of a steady state**.

https://www.fda.gov/downloads/drugs/guidances/ucm377465.pdf

Steady State BE Study Recommendations

PSG Summaries

Product Indications	Total Number (N=49)	Example drugs	PK study & metrics
Oncology	27	Altretamine, Imatinib Mesylate & Bexarotene	Steady state generally achieved within a few days (4-5 half lives) Cmax and AUC and other supportive parameters
Antipsychotic	10	Paliperidone, Risperidone & Clozapine	Similar to above; Except long-acting injectable products
Others (anti-epileptic, and anti-infective)	12	Felbamate & Amphotericin B	

PSG: Product Specific Guidance at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075214.htm

ANDA: Abbreviated New Drug Application; BE: bioequvalence

Long Acting Injectable (LAI) Products

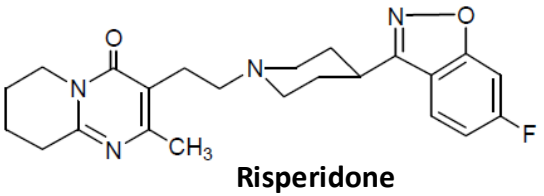
- BE studies are challenging (i.e., time and $$$)
  - Long study duration due to long half-lives
  - Large number of subjects due to high PK variability
  - PSGs generally recommend steady state BE studies in patients due to safety concerns
- BE assessment needs special considerations
  - PSG generally have specific wording on individual steady state attainment
    - Inconsistent assessment methodologies have been proposed
  - Conventional BE assessment methodologies necessitate long BE studies
  - Alternative BE assessment approaches are encouraged

PLGA-based Injectable Depot Formulations

Product Name	Drug	Type	Duration	Dose	Approved
Lupron Depot®	Leuprolide acetate	Microparticle	1,3,4,6 months	7.5 mg/month	1989, 1996, 1997,2011
Zoladex® Depot	Goserelin acetate	Solid implant	1,3 months	3.6 mg/month	1989
Sandostatin LAR®	Octreotide acetate	Microparticle	1 month	10-30 mg/month	1998
Atridox®	Doxycycline hyclate	In situ gel	1 week	42.5 mg/week	1998
Nutropin Depot®	Somatotropin	Microparticle	1 month	13.5 mg/month	1999
Trelstar®	Triptorelin pamoate	Microparticle	1,3,6 months	3.75 mg/month	2000, 2001, 2010
Somatuline® Depot	Lanreotide	Microparticle	1 month	60 mg/month	2000
Arestin®	Minocycline HCl	Microparticle	2 weeks	0.5 mg/week	2001
Eligard®	Leuprolide	In situ gel	1,3,4,6 months	7.5 mg/month	2002
Risperidal® Consta®	Risperidone	Microparticle	2 weeks	12.5 mg/week	2003
Vivitrol®	Naltrexone	Microparticle	1 month	380 mg/month	2006
Ozurdex®	Dexamethasone	Solid implant	3 months	0.23 mg/month	2009
Propel®	Mometasone furoate	Solid implant	1 month	0.37 mg/month	2011
Bydureon®	Exenatide	Microparticles	1 week	2.0 mg/week	2012
Lupaneta Pack™	Leuprolide acetate	Microparticles	3 months	3.75 mg/month	2012
Signifor® LAR	Pasireotide	Microparticles	1 month	20~60 mg/month	2014
Zilretta®	Triamcinolone	Microparticles	3 month	32 mg/3 months	2017
Sublocade™	Buprenorphine	In situ gel	1 month	100, 300 mg/month	2017
Perseris™	Risperidone	In situ gel	1 month	90, 120 mg/month	2018

PLGA: poly(lactic-co-glycolic acid), Courtesy slide from Dr. Yan Wang

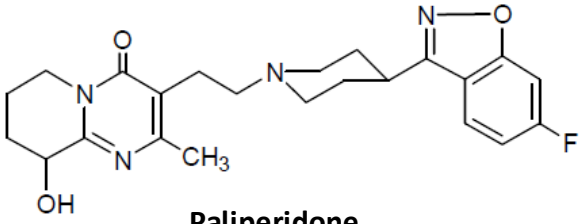
INVEGA SUSTENNA® Background



Risperidone

NDA-20272, 21346

9-hydroxy-metabolite of risperidone

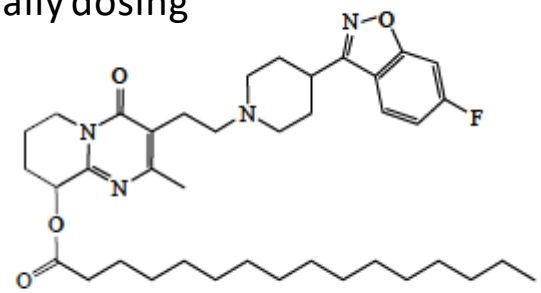


Paliperidone

NDA-21999

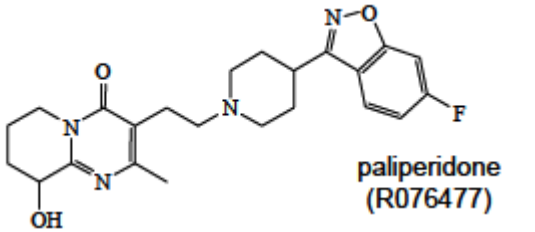
Approved for the treatment of schizophrenia or schizoeffective disorder

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

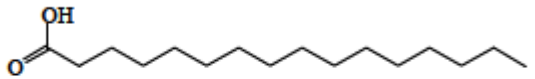


paliperidone palmitate (R092670)

Ester hydrolysis



paliperidone (R076477)



palmitic acid

ER suspension injectable

NDA-22264; Invega Sustenna; every month - 2009

NDA-207946; Invega Trinza; every 3 month - 2015

INVEGA SUSTENNA® Background

- Doses of paliperidone oral tablet and paliperidone long acting injectable needed to attain similar steady-state paliperidone exposure during maintenance treatment

Formulation	Paliperidone ER oral Tablet	Paliperidone LAI
Dosing Frequency	Once daily	Once every 4 weeks
Dose (mg)	12	234
	9	156
	6	117
	3	39-78

- Paliperidone palmitate 39mg/0.25ml, 78mg/0.5ml, 117mg/0.75ml, 156mg/ml, and 234mg/1.5ml hydrolyzes to paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively.

- All the strengths are manufactured from **common bulk suspension, and differ only in the filled volume of suspension in the syringe**.

- The **AUC** of paliperidone following INVEGA® SUSTENNA® administration was **dose-proportional over a 39 mg-234 mg dose range**, and **less than dose-proportional for Cmax for doses exceeding 78 mg**.

Invega Sustenna FDA Label
Clin Pharm Rev

Contains Nonbinding Recommendations

Draft Guidance on Paliperidone Palmitate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Extended-release suspension; intramuscular

Recommended Studies: One study

Type of study: (1) Parallel group, steady-state or (2) two-period, crossover steady-state
Strength: 156 mg/mL
Subjects: Male and nonpregnant female patients with schizophrenia or schizoaffective disorder who are already receiving a stable regimen of paliperidone palmitate extended-release suspension via the intramuscular route. Patients who are already receiving 156 mg of paliperidone injection every month would be eligible to participate in the study if continuing their established maintenance dose.
Additional comments: (1) FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment. (2) Both sites of injection (gluteal and deltoid) should be included in the study design for adequate site representation to support the results of the study. (3) More than three doses may be required to reach steady state. Pharmacokinetic (PK) data should be submitted to demonstrate that steady state has been reached for each individual.

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

Bioequivalence based on (90% CI): Paliperidone

In the evaluation of bioequivalence (BE) of the multiple-dose study, the following PK data should be submitted for paliperidone:

- Individual and mean blood 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_{τ} (AUC_{τ} 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 mean time to peak concentration

The 90% confidence interval for the ratio of the geometric means of the PK parameters (AUC and C_{max}) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with fluctuation of the reference product. The trough concentration data should also be analyzed to verify that steady state was achieved prior to PK sampling.

Frequently Asked Questions in BE Studies

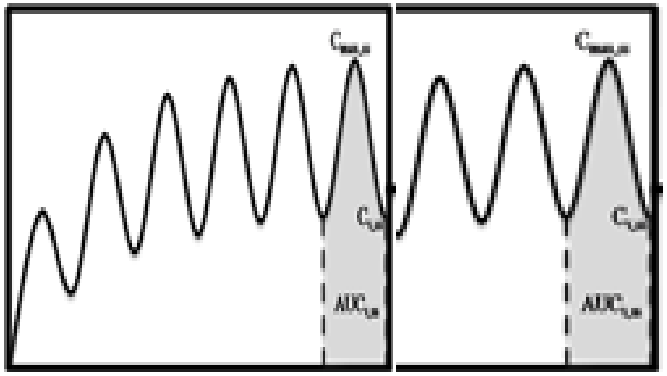
Study Design	1. What is the adequate number of doses to attain and confirm steady state? 2. Is the proposed sample size sufficient? 3. Is a BE study with repeated measurements appropriate? 4. Is open-label BE study appropriate? 5. What is the appropriate dose level to conduct BE studies? 6. Is PK sampling scheme appropriate?
PK analysis	1. Can BE analysis be conducted without distinction between administration sites? 2. Can linear mixed effects model be used to assess the effects of treatment, period, sequence, and injection site? 3. What are appropriate primary and secondary PK endpoints?

Current FDA Assessment Practice

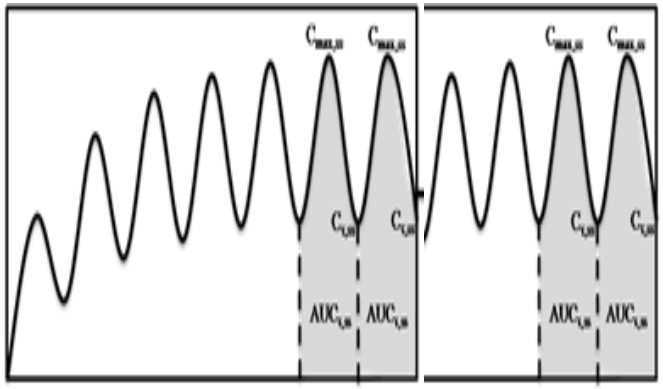
- General procedure for steady state assessment
  - Achievement of steady-state is assessed by comparing at least three pre-dose concentrations for each formulation at individual levels
    - Linear square regression
  - Null hypothesis
    - H0: The variable TIME is insignificant.
    - H1: The variable TIME is significant.
    - Criteria: α=0.05
  - Compare the BE outcome with or without the subjects whose terminal slope is significantly different from 0

Repeated Measurement in BE Study

Conventional Steady State Crossover Design (Sequence: TR / RT)



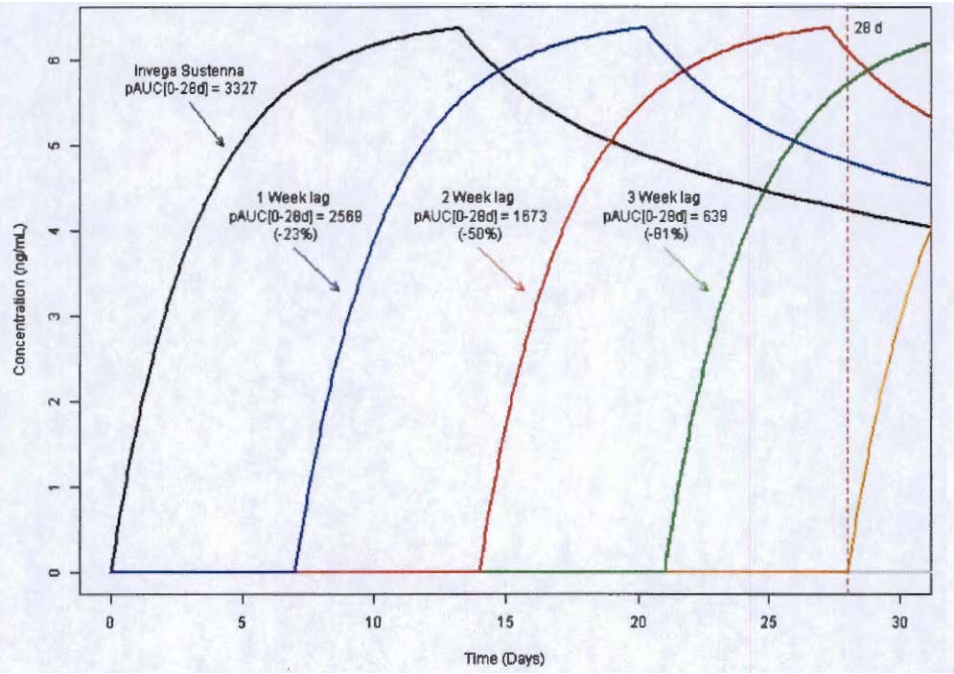
Repeated Measurements with Two Consecutive Administrations (Sequence: TTRR/RRTT)

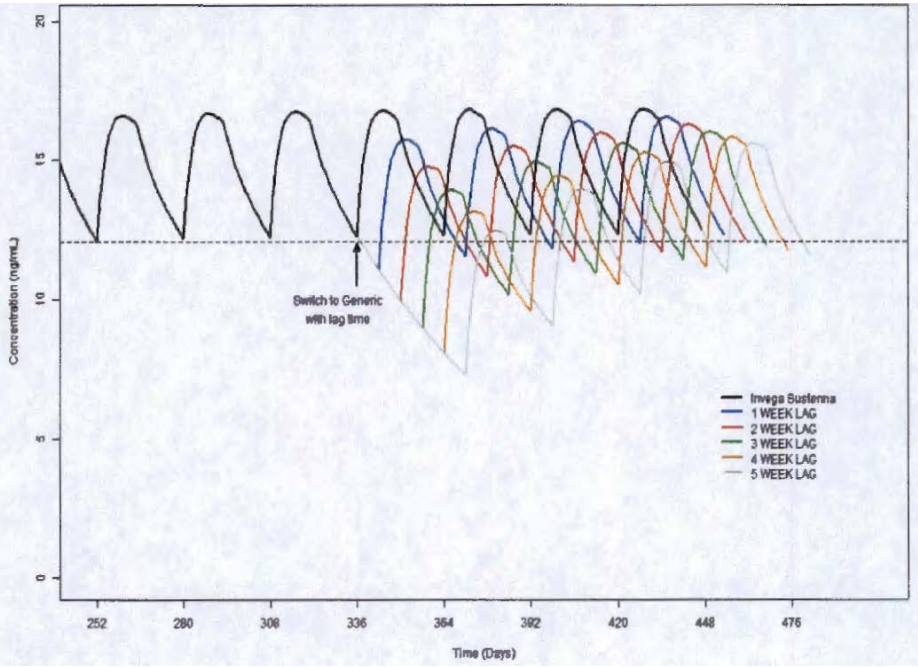


- Example of alternative design to the approach in PSG
- Less number of subjects
- Allow estimation of intra-subjects variability of the formulations
- We encourage you discuss with FDA before implement this design
  - Can this be used for scaled-bioequivalence?

https://www.lambda-cro.com/steady-state-bioequivalence-study-ema-full-replicate-2-period-study-design-with-two-consecutive-day-profile/

Single and Multiple Dose PK of Test Products with Delayed Release



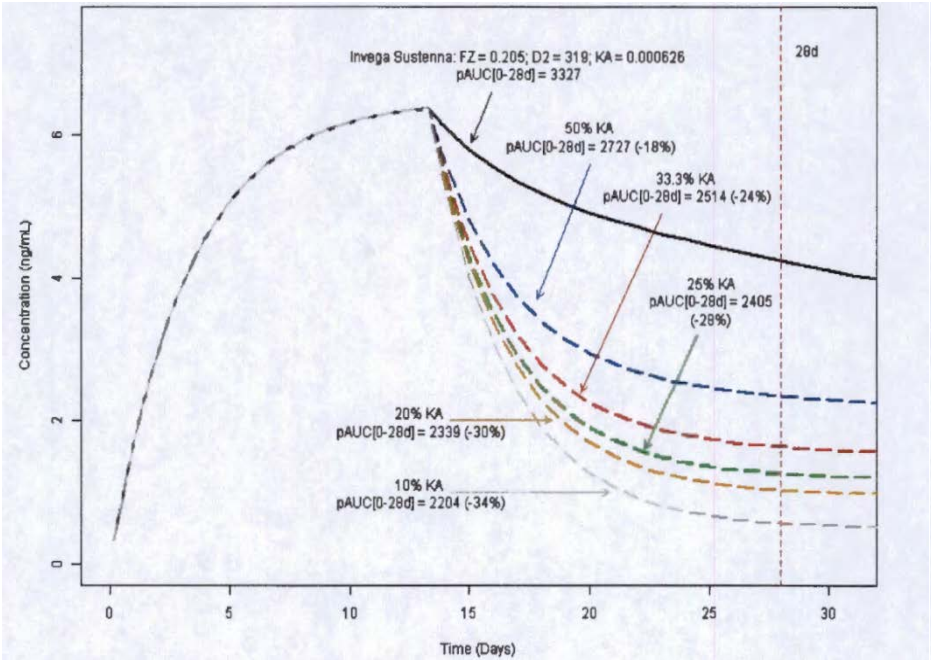


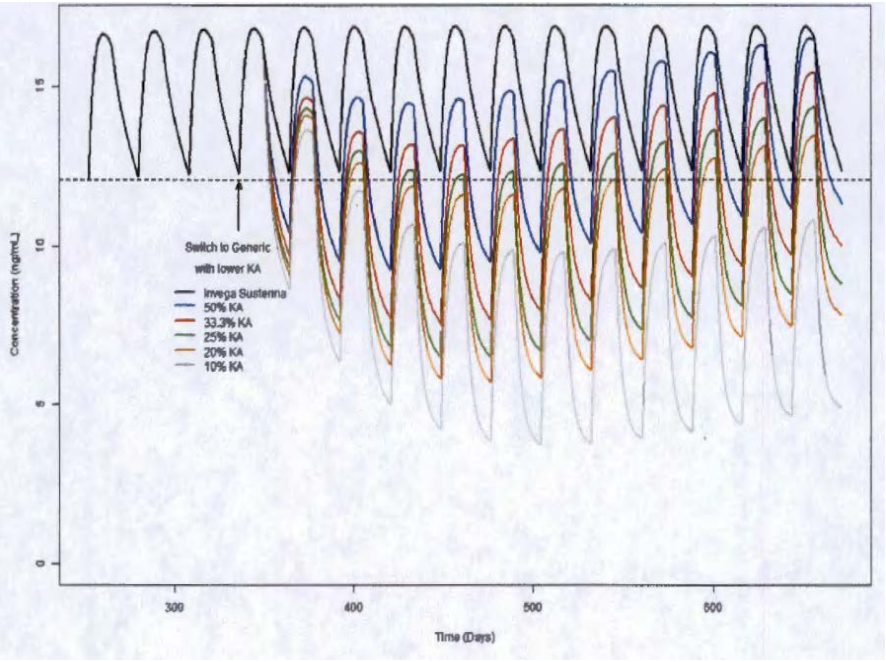
- Conventional BE metrics (Cmax and AUC) cannot differentiate these products with delayed release in SD PK studies
- pAUCs (such as $AUC_{0\text{-}28d}$) can differentiate PK profiles

- 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

Single and Multiple Dose PK of 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

What Would You Do If ….

You have developed a pharmacometric MODEL to support the development and approval of your generic LAI product?

- The pre-ANDA product development meeting is a good venue to discuss your model and its application with OGD prior to ANDA submission

- Example of discussion topics:
  - How model performance/predictability will be assessed?
  - How the model will be verified (including model assumptions, limitations, optimization/refinement)
  - How virtual bioequivalence studies will be conducted? How will the two products (test vs. reference) be defined in the model?
  - Is model-based BE assessment valid?

- Acceptability of your approach will be determined at the time of ANDA review

Take Home Messages

- Steady-state BE studies are generally recommended in patients for safety concerns
- Steady-state BE study design and BE assessment can be challenging for LAI products
  - Clarify your proposed approach to document steady state with FDA via the controlled correspondence or meeting process
- 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

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