Regulatory Considerations in Development of Generic Long-Acting Injectable (LAI) Formulations for HIV Treatment and Prevention

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FDA's Current Thinking on Generic LAIs to Demonstrate Therapeutic Equivalence

Non-complex LAIs (solution)

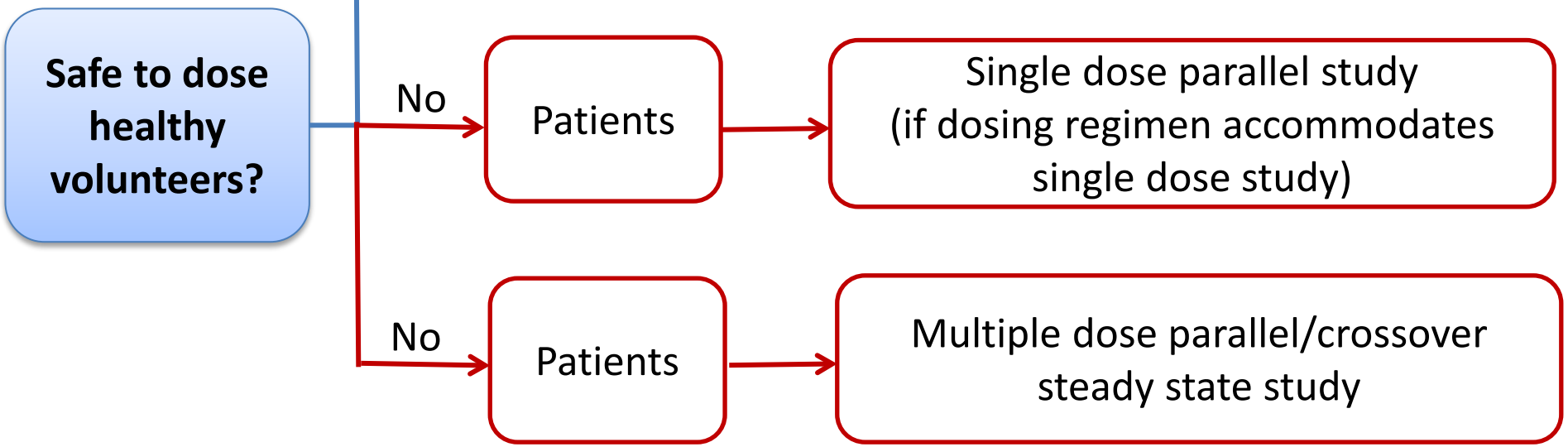
- In vivo BE study waived (320.22(b)(1)).
- Generic approval based on qualitative (Q1) and quantitative (Q2) sameness.

Complex LAIs (non-solution)

- For a parenteral drug product, a generic drug must be Q1 and Q2 the same as the RLD.
- In general, in vivo BE study with PK endpoints is recommended. Additional in vitro characterizations (polymer characterization + IVRT) are needed for certain PLGA microsphere products.
- An in vitro only option [Q1+Q2+comparative physicochemical tests (Q3)/IVRT] is available only for certain products.

RLD: reference listed drug; BE: bioequivalence; PK: pharmacokinetics; IVRT: in vitro drug release test; PLGA: poly(lactide-coglycolide)
Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RLD product

PK BE Studies for LAI Products



- Recommended in PSG for
  - Cabotegravir
  - Medroxyprogesterone acetate
  - Naltrexone
  - Exenatide

- Recommended in PSG for
  - Leuprolide acetate
  - Goserelin acetate
  - Triptorelin pamoate

- Recommended in PSG for
  - Paliperidone palmitate
  - Aripiprazole
  - Risperidone

Partial AUC is recommended in single dose study for certain LAI products based on considerations on clinical relevance/formulation characteristics.

PSG: product-specific guidance

Slide adapted from GBHI 2024 presentation by Yuqing Gong: *Considerations and Challenges of Pharmacokinetics Bioequivalence Studies for LAIs and the Application of Model-Integrated Evidence (MIE) Approaches, Apr. 16, 2024*

FDA Approved LAIs for HIV Treatment and Prevention

Brand Name (Holder)	Active Ingredients	Dosage Form/Route	Indication	Approval Date	PSG Available
CABENUVA KIT (VIIV HLTHCARE)	Cabotegravir; Rilpivirine	Suspension, extended release; Intramuscular	Indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. Recommended dosage – Initiate injections of CABENUVA (600 mg of cabotegravir and 900 mg of rilpivirine) on the last day of oral lead-in and continue with injections of CABENUVA every month or every 2 months thereafter (monthly dosing schedule and every-2-month dosing schedules are available).	01/21/2021	Yes
APRETUDE (VIIV HLTHCARE)	Cabotegravir	Suspension, extended release; Intramuscular	Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition. Recommended dosage – Initiation with a single 600-mg (3-mL) injection given 1 month apart for 2 consecutive months on the last day of an oral lead-in if used or within 3 days and continue with the injections every 2 months thereafter.	12/20/2021	Yes
SUNLENCA (GILEAD SCIENCES INC)	Lenacapavir sodium	Solution; Subcutaneous	Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. Recommended dosage – Initiation with oral tablets and subcutaneous injection, followed by once every 6-months maintenance dosing.	12/22/2022	Yes

PSG for Cabotegravir; Rilpivirine

Recommended Feb 2023

Active Ingredients: Cabotegravir; Rilpivirine

Dosage Form; Route: Suspension, extended release; intramuscular

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, parallel, in vivo
   Strength: Cabotegravir 600 mg/3 mL, rilpivirine 900 mg/3 mL
   Subjects: Male and nonpregnant, non-lactating females, general population.
   Additional comments: Prior to injection of extended-release injectable suspensions, an optional oral lead-in dosing followed by a washout period may be considered to assess the tolerability of cabotegravir and rilpivirine as described in the product label.

Analytes to measure: Cabotegravir in plasma; rilpivirine in plasma

Bioequivalence based on (90% CI): Cabotegravir; rilpivirine

Waiver request of in vivo testing: 400 mg cabotegravir, 600 mg rilpivirine based on (i) acceptable bioequivalence study on the 600 mg cabotegravir, 900 mg rilpivirine strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- The product's long-acting feature is based on the extremely low aqueous solubility of each drug substance and slow diffusion at intramuscular site of injection.
- The drug product exhibited flip-flop kinetics with prolonged apparent terminal half-lives (half-life of cabotegravir is 5.6-11.5 weeks, half-life of rilpivirine is 13-28 weeks).
- A single dose crossover design is not practical due to the long washout period. Therefore, a parallel design is recommended.
- Given the feasibility of conducting the BE study in healthy subjects, a single dose BE study in general population is recommended.

FDA's PSG for Generic Drug Development available at:
https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

PSG for Cabotegravir

Recommended May 2023

Active Ingredient: Cabotegravir

Dosage Form; Route: Suspension, extended release; Intramuscular

Strength: 600 mg/3 mL

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, parallel, in vivo
   Strength: 600 mg/3 mL
   Subjects: Male and non-pregnant, non-lactating females, general population.
   Additional comments: Prior to injection of cabotegravir extended-release injectable suspension, an optional oral lead-in dosing followed by a washout period may be considered to assess the tolerability of cabotegravir as described in the product label.

Analyte to measure: Cabotegravir in plasma

Bioequivalence based on (90% CI): Cabotegravir

Waiver request of in vivo testing: Not applicable

- Similar to cabotegravir; rilpivirine suspension, the long-acting feature is based on the extremely low aqueous solubility of cabotegravir and slow diffusion at intramuscular site of injection.
- The recommendation aligns with the PSG of cabotegravir; rilpivirine suspension.

PSG for Lenacapavir

Recommended Feb 2024

Active Ingredient: Lenacapavir sodium

Dosage Form: Solution

Route: Subcutaneous

Strength: EQ 463.5 mg Base/1.5 mL (EQ 309 mg Base/mL)

Recommended Study: Request for waiver of in vivo bioequivalence study requirements

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant provided the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[3]

Rationale of waiving in vivo BE study:

- Dosage form is solution
- Composition does not contain any release controlling excipients
- Long-acting properties are not related to the formulation

Modeling and Simulation as Modern Tools for Drug Development

- Modeling and simulation makes drug product development and regulatory assessment more efficient
  - MIDD: M&S an integral part of new drug development for almost all NME NDAs and BLAs
    - PDUFA VI: MIDD paired meeting pilot
    - PDUFA VII: Officially part of the user fee act
  - MIE: Can cover all challenging areas for generic drug development, especially for complex generics
    - GDUFA III: MIE Industry Meeting pilot launched on October 1st, 2023
- New modeling types and utilities (e.g., QSP and AI/ML, etc.)

MIDD: Model-Informed Drug Development; **MIE: Model-Integrated Evidence**; QSP: Quantitative Systems Pharmacology; AI/ML: Artificial Intelligence/Machine Learning
MIE pilot: https://www.fda.gov/media/172028/download?attachment

Opportunities for Model-Integrated Evidence (MIE) Approaches in Generic LAI Development

- Enhance the efficiency of PK BE studies: alternative designs with shorter study duration and/or smaller sample size supported by MIE
  - **Early truncation of single dose PK study**
  - Carryover adjustment to allow crossover design with incomplete washout over parallel design
  - Optimal study design strategies
- Mechanistic in vitro-in vivo correlation (IVIVC) modeling to support risk assessment of deviations in *in vitro* characterizations;
- Physiologically based pharmacokinetic modeling informed by *in vitro* characterization data and a small-scale in vivo PK study to reduce the recruiting burden
- We see a clear demand: increased use of modeling approaches in pre-ANDA meeting requests and ANDA submissions

MIE to Support BE Evaluation with An Incomplete Washout Design

(FDA Contract 75F40122C00139 with Uppsala University)

- FDA is collaborating with Uppsala University to develop more feasible BE study designs for highly variable drugs (HVDs) with long half-lives.
- Preliminary results showed that MIE together with reference-scaled average BE (RSABE) analysis are flexible enough for analyzing data from both conventional BE designs with a complete washout and novel BE designs with an incomplete washout (adequate study power and Type I error control).
- Simulations showed that the incomplete washout design reduces ~70% of overall study duration.

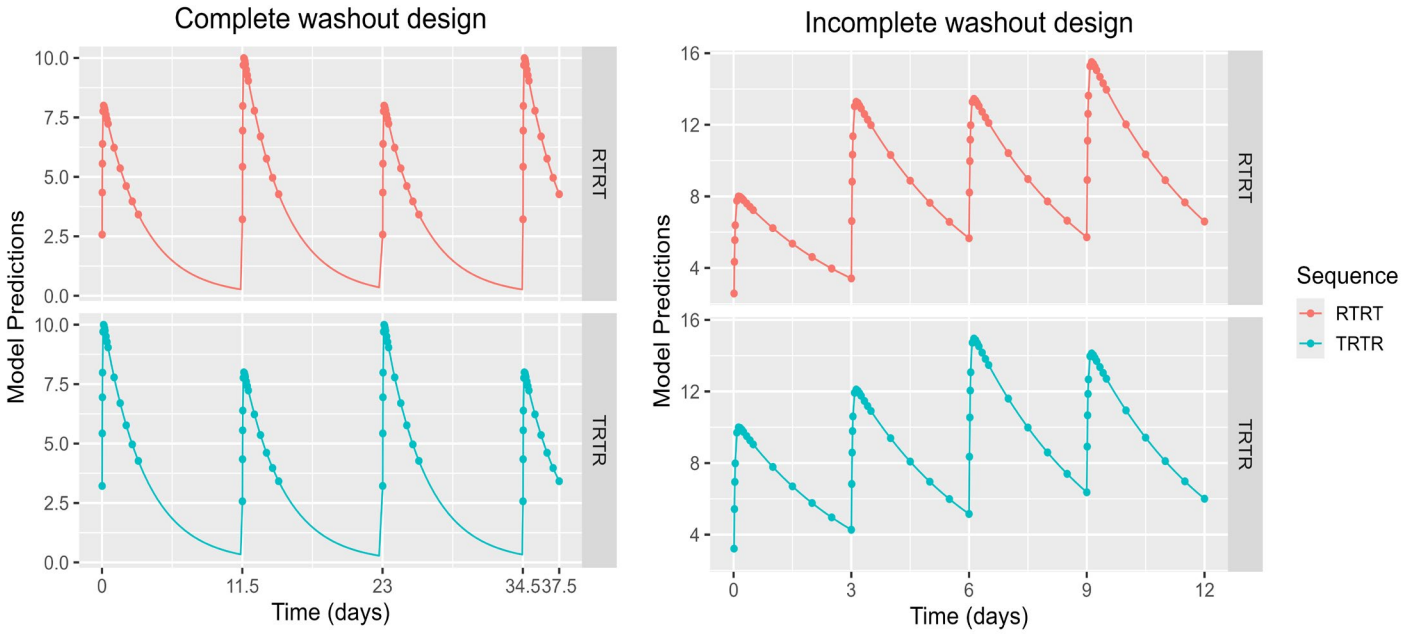


Figure. Simulations of an example long half-life drug

Huang Z, et al.. *Model-Integrated Bioequivalence Method for Highly Variable Drugs with Long Half-Life: a Simulation Study Comparing Complete Washout and Incomplete Washout Designs*. Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. Rome, Italy, Jun. 26, 2024.

Summary and Resources

- FDA continues to improve PSGs based on updated understanding obtained through communications with generic industry (via public workshop, pre-ANDA interactions) and Generic Drug User Fee Amendments (GDUFA) funded research.
  - PSG Database
  - FY 2023 GDUFA Science and Research Report
  - Educational events and workshops hosted by FDA and Center for Research on Complex Generics (CRCG)
- Generic applicants are encouraged to develop alternative BE approach (e.g., alternative design supported by MIE) and engage with the Agency early during development.
- **Contacts:**
  - Pre-ANDA Meetings Program for Complex Generic Products. For questions about submitting Pre-ANDA meeting requests, please contact PreANDAHelp@fda.hhs.gov.
  - Specific questions regarding the MIE approaches can be submitted to the MIE Pilot Program. Questions about the program may be directed to MIE@fda.hhs.gov.

ANDA: abbreviated new drug application

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