Regulatory Considerations in Development of Generic LAI Formulations for HIV Treatment and Prevention

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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.

Long-Acting Injectables (LAIs)

LAIs provide sustained and continuous release of drug substance over a period of days to months when administered via intramuscular, subcutaneous, epidural, and intra-articular routes.

LAIs improve compliance and treatment adherence by reducing dosing frequency through maintenance of plasma drug concentrations over a longer time period than other dosage forms.

Example therapeutic areas: antipsychotic, hormonal therapy, substance abuse disorders.

For most LAIs, there is no generic approval to date.

Objectives

- An overview of drug approval process under FD&C Act
  - 505(b)(1) NDA
  - 505(b)(2) NDA
  - 505(j) ANDA
- Framework and differences between three regulatory pathways
- Bioequivalence (BE) considerations for LAIs
- Future Next Steps

FD&C Act: Federal Food, Drug, and Cosmetic Act
NDA: New Drug Application
ANDA: Abbreviated New Drug Application

Types of Applications

505(b)(1) NDA: A novel drug/active ingredient never been studied or approved by FDA

- Application contains full reports of investigations of safety and effectiveness
- Applicant owns or has right of reference to all reports – "stand-alone"

505(b)(2) NDA: Modifications of a drug already approved (e.g. new dosage forms, strength, route of admin, formulation, dosing regimen, combination with other products, new indication)

- Application contains full reports of investigations of safety and effectiveness
- Applicant does not own or have right of reference to at least some information required for approval
- Permits reliance on literature or Agency's findings of safety and/or effectiveness for a previously approved drug product

Example: Tenofovir DF, lamivudine, dolutegravir (TLD)

ANDA 505(j): Generic Products - Duplicates of previously approved drugs and provides information to show proposed product is the same as a Referenced Listed Drug (RLD, approved product)

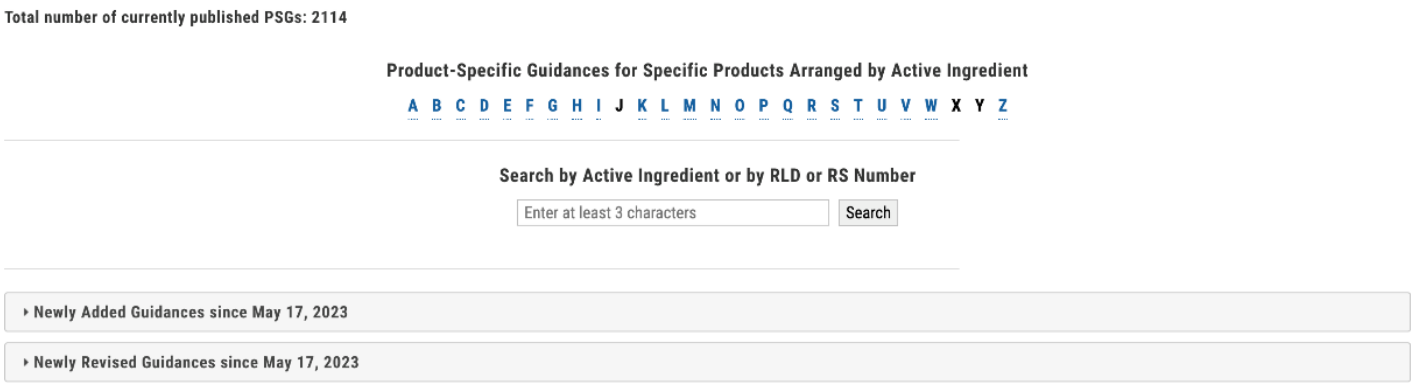
- Relies on FDA's finding that the previously approved RLD is safe and effective
- Must demonstrate pharmaceutical equivalence and bioequivalence of generic drug to RLD/RS
- To establish BE, the calculated confidence interval must fall within a BE limit: 80-125% for the ratio of the product averages

Regulatory Considerations for ANDAs

- Generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the reference listed drug. However, differences in preservative, buffer, and antioxidant are allowed if appropriately justified by the applicant [per 21CFR §314.94].

Product-Specific Guidance (PSG) for Generic Drug Development

- FDA program led by ORS (PSG Team)
- Reflects FDA's current thinking and expectations on how to develop a generic drug product that is therapeutically equivalent to a specific Reference Listed Drug
- Assists generic drug applicants with identifying the most appropriate methodology and studies for approval
  - In vivo and/or in vitro bioequivalence (BE) studies, waiver options (BCS – biopharmaceutics classification system-based waiver) and dissolution testing



Adopted by: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Summary

	505(j) ANDA generic	505(b)(1)	505(b)(2)
New active ingredients	x	✓	✓/x
New formulation	x	✓	✓/x
New indication	x	✓	✓
Eligible for patent Listing in Orange Book	x	✓	✓
Studies	BE/BA	Full	Partial

Bioequivalence (BE) Study Recommendations for LAIs

- Depending on the specific LAI, one of the following approaches may be recommended to demonstrate BE between test product and reference standard:
  - In vivo BE study with PK endpoints + qualitative (Q1) and quantitative (Q2) sameness
  - In vitro studies in combination with an in vivo PK BE study: Q1 and Q2 sameness + comparative in vitro physicochemical characterization (Q3) + comparative in vitro drug release testing + in vivo PK BE study
  - In vitro studies as an alternative to an in vivo BE study based on a totality of evidence approach for Q1/Q2 generic formulations: comparable Q3 characteristics + comparable in vitro drug release profile

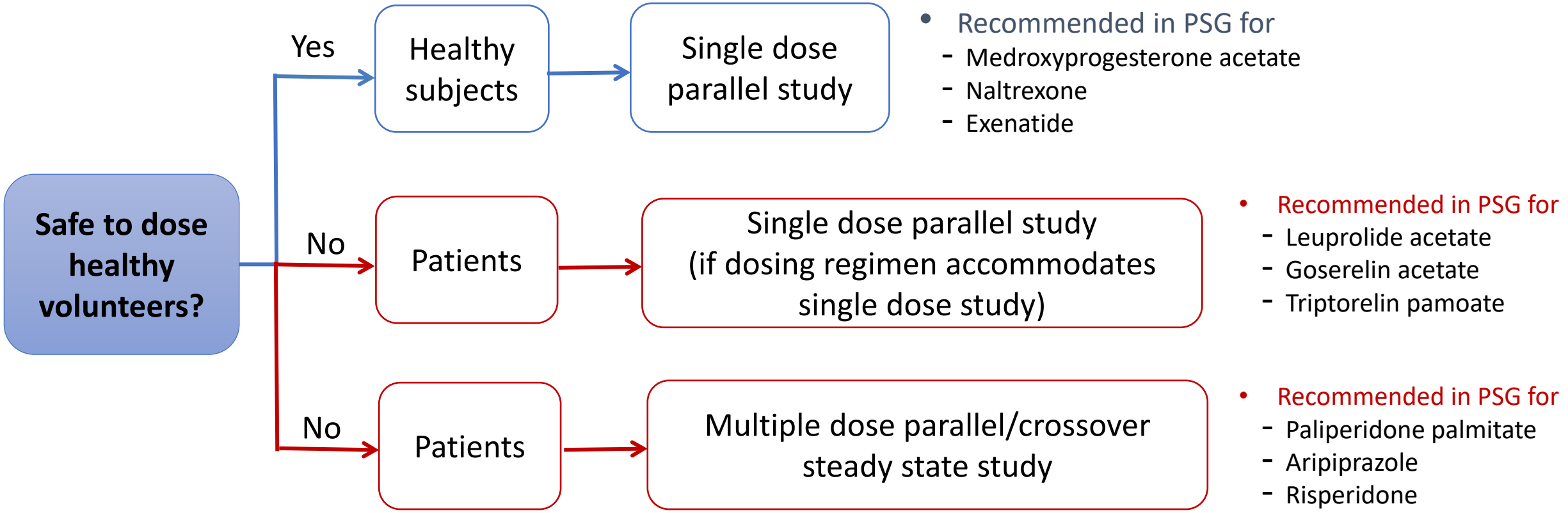
Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RLD product

BE Study Recommendations – Example Product-Specific Guidance (PSG) for LAIs

LAI drug product	BE recommendation in PSG
Medroxyprogesterone Acetate Injectable Suspension	In vivo single-dose parallel BE study with PK endpoints
Risperidone Injection	Q1/Q2 sameness, physicochemical characterization of PLGA, in vitro drug release testing, and in vivo crossover steady-state BE study with PK endpoints
Penicillin G Benzathine Injectable Suspension	Two options • In vitro option: Q1/Q2 sameness, physicochemical characterization, and in vitro drug release testing • In vivo option: single-dose parallel BE study with PK endpoints

FDA's Product-Specific Guidance (PSG) for Generic Drug Development available at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

FDA Recommended BE Studies for LAI Products



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

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

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

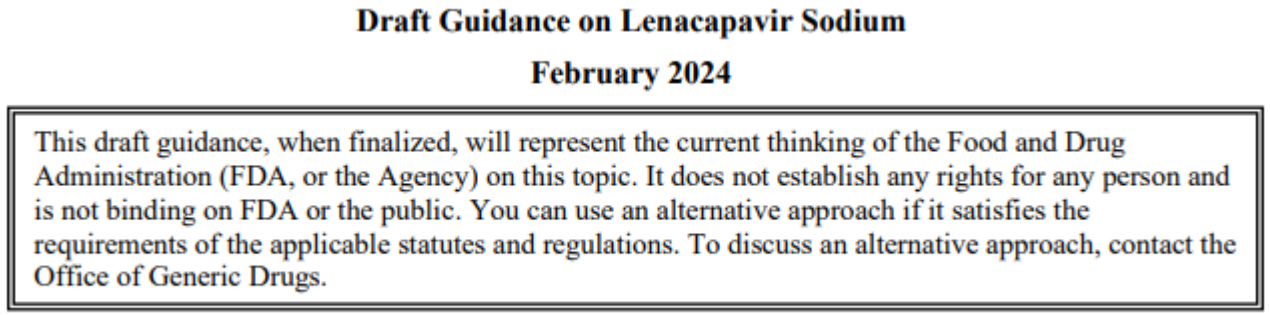
Partial AUC is recommended in single dose study for certain LAI products based on considerations on clinical relevance/formulation characteristics.

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*

Lenacapavir Draft Product-Specific Guidance

- **Recommended Study**: Request for waiver of in vivo BE study requirements
- To qualify for a waiver from submitting a BE study, the test product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD
- Rationale:
  - Dosage form is solution
  - Composition does not contain any release controlling excipients
  - Long-acting properties are not related to the formulation



Draft Guidance on Lenacapavir Sodium

February 2024

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.

General Considerations in the Study Design of In Vivo BE Studies for LAIs

Crossover vs. Parallel Design:

- Generally parallel design for single dose study to avoid washout concerns due to long half-life
  - medroxyprogesterone acetate injectable: approximately 50 days
  - naltrexone: 5-10 days
- Parallel or crossover design for steady state study

Strength to be studied:

- In general, highest strength is recommended unless safety concern
- Multiple strengths may be recommended in some cases
- For certain LAI products (e.g., risperidone injection), any strength may be used

PK Metrics:

- Single dose study: Cmax, AUCt, AUCinf, Tmax
- Multiple dose study: Cmax, AUCtau, Tmax, Cmin, Fluctuation
- Partial AUC based on clinical relevance and formulation characteristics, e.g., Naltrexone ER injectable suspension: inclusion of AUC1-10 and AUC10-28 to account for multi-phasic release profile and therapeutic threshold
- Cmax and AUCs are subject to 90% confidence interval between 80-125%

General Considerations in the Study Design of In Vivo PK Studies for LAIs

Injection site:

- Based on RLD information (e.g., labeling), either gluteal or deltoid sites are included in the study design for adequate administration site representation. If both sites of injection (gluteal and deltoid) are included in the study, proportions of the patients should be similar between test and reference group

Steady-state:

- Sufficient number of doses should be administered to achieve steady-state (e.g., antipsychotic injectables)

Challenges in the Conduct of In Vivo BE PK Studies for LAIs

- Recruiting difficulty
- Long study duration
- High dropout
- High variability for parallel study
- Variability being contributed from multiple factors (demographics, clinical center, etc.)
- Steady state determination
- Safety concerns
- Reserve sample retention

Key Takeaways for In Vivo BE Study Design and Conduct for LAIs

- Overall BE study design for LAIs should account for the formulation design (i.e., release-controlling mechanism), dosing regimen/frequency and the study population
- Appropriate number of doses to achieve steady-state should be determined and balanced by need to minimize study duration
- Consideration of dropout rate in sample size estimation
- Appropriate sampling scheme to accurately capture PK parameters
- Sufficient pre-study method validation examining interference of concomitant meds
- Appropriate safety monitoring
- Appropriate statistical approach for evaluation of demographics and clinical center effect as needed

Next Steps

- Based on the November 2021 FDA and Center for Research on Complex Generics hosted workshop: Establishing the Suitability of Model-Integrated Evidence (MIE) to Demonstrate BE for LAIs
- New/alternative approaches such as MIE to accelerate development of generic LAIs
- MIE could reduce in vivo study duration and/or sample size and may justify use of alternative study designs and/or alternative BE metrics through the model-based BE analysis framework
  - Important consideration is using MIE for BE is to demonstrate its sensitivity to detect the formulation difference with confidence
  - Need for sufficient model verification and validation
- MIE has been used in new drug development e.g., optimize dosing regimens, define dosing windows, select re-initiation plans and dose adjustment in subgroups

Model-Informed and Model-Integrated Approach

- **Model-Informed**
  - Modeling and simulation to inform study designs, analysis methods
  - Aid in product development and help in decision making
  - Help design and justify appropriate sampling strategy

- **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 BE study
  - In combination with relevant in vitro BE tests, support alternative to otherwise recommended in vivo BE studies, including but not limited to PK, PD or comparative clinical endpoint BE studies

- Both approaches can help in reducing study durations and/or sample size, which can help in designing a more feasible BE study for LAI product
  - FDA awarded approximately 39 research contracts and 50 grants for model-related research relevant to establish bioequivalence.

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

Opportunities for MIE in Generic LAI Development

- Two different strategies for alternative BE approaches supported by MIE
  - Enhance the efficiency of PK BE studies (e.g., alternative design strategies) supported by population PK modeling to help in reducing study durations and/or sample size, which can help in designing a more feasible BE study for LAI product.
  - BE based of in vitro characteristics/studies in lieu of conducting PK BE studies mediated through mechanistic modeling such as physiologically based PK (PBPK) modeling
- Generate pivotal evidence through MIE for BE decision via:
  - a prespecified model-based analysis of an in vivo BE study
  - a virtual bioequivalence (VBE) study
- We see a clear demand: increased use of modeling approaches in pre-ANDA meeting requests and ANDA submissions

Slide adapted with revisions from presentation by Andrew Babiskin at CRCG 2024 Workshop: Considerations and Potential Regulatory Applications for a Model Master File. *Regulatory Utility of MMF for Development of Long-Acting Injectable Drug Products, May. 2, 2024*

Resources

- Draft Guidance for Industry Population Pharmacokinetics (2019)
- Guidance for Industry Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications (2003)
- Draft Guidance for Industry Adaptive Designs for Clinical Trials of Drugs and Biologics (November 2019)
- Leveraging Quantitative Methods in Reviewing Complex/Locally Acting Products (October 2-3, 2017)
- 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.

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Thank You!