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"Regulatory considerations in the development of generic LAI formulations"

"[The Office of Generic Drugs] is very excited to work with developers in this field for LA ARVs"

Most LAI products have no generic approvals to date

- LAIs maintain drug plasma concentration longer than other dosage forms (i.e., Sustained continuous drug release over days to months).
- Reduced dosing frequency improves compliance and treatment adherence.
- Low-cost, generic LAI ARV formulations are needed to optimize HIV prevention and treatment in LMICs.

New drug application (NDA) pathways under the FDC act

Novel drugs and Modifications of approved drugs.

NDA 505(b)(1) Novel Drug	NDA 505(b)(2) Modification of Approved Drug
Drug/active ingredient that has never been studied or FDA approved.	New dosage form, strength, route, formulation, dosing regimen, combination, or indication for an FDA-approved/reference listed drug (RLD).
Applicant owns or has right of reference to all reports, including P1-3, non-clinical, and CMC packages.	Applicant does NOT have right of reference to at least some of the information required for approval
Stand-alone application.	Typically permits reliance on the literature or prior FDA review for non-clinical information plus submission of additional P1 or 2 data.
No other regulatory considerations.	**Drug product cannot have existing patents or exclusivity**.

Generic drug products.

Abbreviated NDA (ANDA) 505(j) Generic Drug
Copycat of a RLD.
Approval relies on prior FDA review of safety and efficacy information for the approved drug.
Applicant must show pharmacological equivalence and bioequivalence (i.e., Therapeutic equivalence) of the proposed drug to the RLD.
All FDA-approved drugs have a product-specific guidance (PSG) for demonstrating bioequivalence (BE).
BE limit: The calculated CI for the ratio of product averages must fall within 80-125%.
Parenteral products: Proposed and reference drug products must contain the same inactive ingredients and in the same concentrations; Differences in preservatives, buffer and antioxidant are allowed if appropriately justified.

PSGs support generic drug approval

PSG reflects current FDA expectations for showing TE.

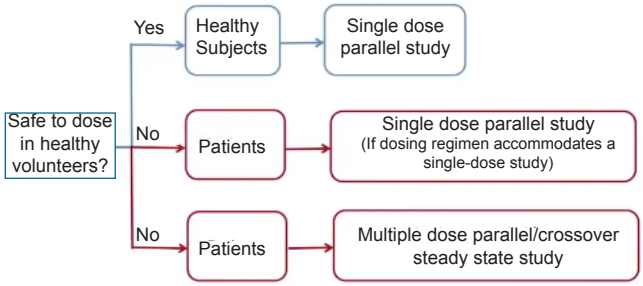
- A draft PSG is issued for every newly approved drug.
  (Available at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm).
- Informs the most appropriate data and methodologies for approval.
  - ◊ In vitro +/- in vivo testing; Dissolution testing; Biopharmaceutical classification system (BCS)-based waiver.

Recommended BE approach depends on the specific LAI.

- In vivo PK BE study + Q1 and Q2 sameness.
  - ◊ Q1 (Qualitative) sameness: Test and RLD product contain the same inactive ingredients.
  - ◊ Q2 (Quantitative) sameness: Concentrations of inactive ingredients in the test and RLD product are within 5%.
- In vivo PK BE study + Q1 and Q2 sameness + Q3 similarity + comparable in vitro release profile.
  - ◊ Q3 similarity: Test and RLD product have no structural and physiochemical differences that would significantly impact bioavailability (BA).
- Q3 similarity + comparable in vitro release profile (No in vivo study).
  - ◊ May be possible for Q1/Q2 formulations based on a totality of the evidence approach.

Recommended BE study design.

- Study population depends on drug/AI safety.



- SD parallel study in HVs: PSG for Medroxyprogesterone acetate, Naltrexone, Exenatide.
- SD parallel study in patients: PSG for Leuprolide acetate, Goserelin acetate, Triptorelin acetate.
- MD parallel/crossover study in patients: PSG for Paliperidone palmitate, Aripiprazole, Risperidone.

Sample PSGs for FDA-approved LAIs

Reference Listed Drug	Product-Specific Guidance
Medroxyprogesterone acetate injectable suspension	In vivo SD parallel BE study with PK endpoints.
Risperidone injection	Q1/Q2 sameness + Q3 characterization of PGLA + in vitro drug-release testing + in vivo crossover steady-state BE study with PK endpoints
PEN-G benzathine injectable suspension	Option 1: Q1/Q2 sameness + Q3 characterization + in vitro drug-release testing
	Option 2: SD parallel BE study with PK endpoints

Summary

- Today's meeting is focused on development of generic LAI products (i.e., Copycats, not modifications of FDA-approved drugs).
  - ◊ There is also much interest in developing formulations of FDA-approved drugs with longer dosing intervals, which is a different application type: NDA 505(b)(2).
- ANDA 505(j) pathway for generic drug approval.
  - ◊ **Not appropriate for new AIs, formulations, or indications.**
  - ◊ Approval relies on bioavailability and BE studies.
  - ◊ FDA PSGs provide recommendations for the type of data and studies required for approval.