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Draft Guidance on Leuprolide Acetate

August 2026

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Active Ingredient:	Leuprolide acetate
Dosage Form:	Powder
Route:	Subcutaneous
Strength:	7.5 mg
Reference Listed Drug:	NDA 021343
Recommended Studies:	Two options: (I) One in vitro bioequivalence study with comparative characterization studies or (II) one in vivo bioequivalence study with pharmacokinetic endpoints

Eligibility: To demonstrate bioequivalence following either Option I or Option II in this guidance, the test and reference listed drug (RLD) formulations should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same. To support Q1 sameness of poly(lactide-co-glycolide) (PLGA), provide comparative characterization data of polymer composition (molar ratio between lactide and glycolide), molecular weight and weight distribution, and architecture (e.g., linear or branched) of the PLGA polymer extracted from the test product and RLD.

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[2] 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.

Option I: One in vitro bioequivalence study with comparative characterization studies

1. Class of study: Bioequivalence
   Type of study: In vitro drug release testing (IVRT)
   Design: Comparative
   Strength: 7.5 mg
   Analytes to measure: Leuprolide and N-methyl-2-pyrrolidone (NMP) in the release medium
   Bioequivalence based on: Cumulative release of leuprolide
   Study design recommendations:
   - The IVRT method should be properly developed and validated, and the method should be able to detect and discriminate potential formulation differences, such as variations in polymer characteristics or drug loading.
   - Details on sample preparation should be provided in method development and validation report.
   - The method should capture the complete release profile of leuprolide.
   - Equivalence in leuprolide release should be established using a proper statistical method.
   - As part of the IVRT study, NMP release from the test and RS products should be monitored and submitted as supportive information.

2. Class of study: Comparative characterization
   Type of studies: Characterization studies for the following physicochemical and structural (Q3) attributes:
   - Visual appearance of leuprolide acetate and polymer-NMP solution supplied in the two syringes (prior to mixing)
   - Viscosity of the polymer-NMP solution (prior to mixing)
   - Visual appearance of the reconstituted drug product
   - Viscosity of the reconstituted drug product
   - Delivered mass of the reconstituted drug product
   - Leuprolide content in the reconstituted drug product measured at 30 min after mixing

   Design: Comparative
   Strength: 7.5 mg
   Study design recommendations:
   - Conduct each characterization test with a minimum of three batches of the test product and three batches of the reference standard (RS).
   - Drug product reconstitution for comparative characterization studies should follow the Instructions for Use provided in the drug product labeling.

3. Class of study: Polymer characterization
Type of studies:
- Molecular weight and weight distribution
- Polymer composition (molar ratio between lactide to glycolide)
- Polymer end cap
- Glass transition temperature
- Intrinsic viscosity

Design: Comparative
Strength: 7.5 mg
Study design recommendations:
- Characterization of PLGA polymer extracted from three batches each of the test product and the RLD.
- Provide sufficient validation data for the methods used for comparative characterization of PLGA in the abbreviated new drug application (ANDA).

Option II: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Class of study: Bioequivalence study with pharmacokinetic (PK) endpoints
Design: Single-dose, randomized, parallel, in vivo
Strength: 7.5 mg
Dose: 7.5 mg
Subjects: Prostatic carcinoma patients undergoing initial therapy or receiving a stable regimen of leuprolide acetate (7.5 mg) via subcutaneous injection
Study design recommendations:
- The test and reference groups should be balanced with respect to patient disease progression and treatment history.
- The same injection site should be used for test and reference products, which should be pre-specified prior to conducting the study.
- The study should include exclusively prostatic carcinoma patients undergoing initial therapy or exclusively those receiving a stable regimen of leuprolide acetate (7.5 mg) via subcutaneous injection route. If both types of patients are included in the study, proportions of the patients should be similar between test and reference groups.

Safety recommendation:
- For prostate carcinoma patients undergoing initial therapy, after the pharmacokinetic study is completed, the treatment should not be discontinued or delayed for a second dose.

Analyte to measure: Leuprolide in plasma

Bioequivalence based on (90% CI): Leuprolide

The 90% confidence intervals of the following PK parameters should meet the acceptable limits of [80.00-125.00]: Log-transformed $AUC_{7\text{-}t}$, $AUC_{0\text{-}t}$, and C_{max}, where $AUC_{7\text{-}t}$ is the area under the plasma-concentration vs. time curve from 7 days to the last sampling time point, $AUC_{0\text{-}t}$ is the area under the curve from 0 to the last sampling time point, and C_{max} is the maximum plasma concentration. Note that the last sampling time point 't' equals the dosing interval of the product used in the in vivo PK study.

Additional recommendations for both Options:

Quality assessment:

1. A minimum of two lots of the PLGA excipient should be used to prepare the three primary batches of drug product.
2. To support quality assessment of the PLGA excipient, provide the following data:
    a. Polymer composition (molar ratio between lactide to glycolide)
    b. Molecular weight and weight distribution
    c. Inherent viscosity
    d. Glass transition temperature
    e. Residual monomer contents
3. In vitro release testing method and sampling times: Conduct comparative in vitro drug release testing on 12 dosage units each of both strengths of the test product and RLD and develop appropriate specifications for quality control purpose. The prospective applicant may use the same or different in vitro release testing method used for establishing bioequivalence for quality control purpose. An accelerated method may be acceptable when properly developed and validated with sufficient justification.

Device: The RLD is presented in a kit that consists of a syringe-mixing system (two syringes and coupling device) and injection needle with needle guard. The syringe-mixing system and injection needle with needle guard are the device constituent parts. FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices including:

- Single-dose, fixed-dose, pre-connected prefilled syringe format
- Needle gauge and length
- Needle guard system

User interface assessment: An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Document History: Recommended August 2021; Revised August 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.