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Draft Guidance on Triamcinolone Acetonide

November 2022

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In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Triamcinolone acetonide
Dosage Form; Route:	For suspension, extended release; intra-articular
Strength:	32 mg/vial
Recommended Studies:	One in vitro bioequivalence study on drug release testing, one in vivo bioequivalence study with pharmacokinetic endpoints, and supportive comparative characterization studies

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

1. Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD)
2. Acceptable comparative physicochemical characterizations of the test and Reference Standard (RS) products. The comparative study should be performed on at least three batches of both the test and RS products and at least one test batch should be used in the in vitro and in vivo bioequivalence studies. The attributes to be characterized should include:
 - a. Polymorphic form of triamcinolone acetonide
 - b. Drug loading, morphology, particle size and size distribution of triamcinolone acetonide microspheres
 - c. Free triamcinolone acetonide dissolved in the diluent upon reconstitution
 - d. pH, osmolality, and viscosity of the reconstituted product
 - e. Characterization data on poly(lactide-coglycolide) (PLGA) extracted from both the test and reference products including lactide to glycolide ratio, molecular weight and weight distribution, inherent viscosity, glass transition temperature (T_g), end cap, and PLGA architecture (e.g., linear or star-branched PLGA)

One in vitro bioequivalence study on drug release testing:

1. Type of study: In vitro bioequivalence study on drug release of triamcinolone acetonide from the test and RS products.
Design: A properly developed and validated method that can detect potential formulation differences and capture the complete release profile of triamcinolone acetonide
Additional comments:
 - a. Equivalence in triamcinolone acetonide release should be established using a proper statistical method. One suggested approach is a model independent similarity (f2) factor. For more information on calculation of f2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.^a
 - b. The same batch should be used for establishing equivalence in triamcinolone acetonide release and the in vivo bioequivalence study.

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, randomized, parallel, in vivo
Strength: 32 mg/vial
Subjects: Patients with osteoarthritis of the knee

Analyte to measure: Triamcinolone acetonide in plasma

Bioequivalence based on (90% CI): Triamcinolone acetonide

The 90% confidence intervals of the following pharmacokinetic parameters should meet the acceptable limits of [80.00-125.00]: Log-transformed $AUC_{0\text{-week}4}$, and C_{\max} , where $AUC_{0\text{-week}4}$ is the area under the plasma-concentration vs. time curve from 0 to week 4, and C_{\max} is the maximum plasma concentration.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

Additional information:

Device:

The RLD is co-packaged in a kit containing a vial with the drug in powder form, a vial of diluent, and a sterile vial adapter. The device constituent is the vial adapter.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test (T) device.

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 most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^a

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^a For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.