Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Dexamethasone; Tobramycin

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

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 Ingredients:	Dexamethasone; Tobramycin
Dosage Form:	Ointment
Route:	Ophthalmic
Strength:	0.1%; 0.3%
Recommended Studies:	Two options: (1) one in vitro bioequivalence study with supportive comparative studies, or (2) one in vitro bioequivalence study and one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: One in vitro bioequivalence study with supportive comparative studies

To demonstrate bioequivalence by this option, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[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 product.
[3] For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. *ANDA Submissions – Refuse-to-Receive Standards: Guidance for Industry.*

One in vitro bioequivalence study:

1. Type of study: In vitro drug release testing (IVRT) of dexamethasone and tobramycin
   Design: Should be performed on three batches of both test and reference standard (RS) products using at least 12 units from each batch
   Strength: 0.1%; 0.3%
   Additional comments: The IVRT method study should include information on the method development and validation to detect potential formulation differences and capture the complete release profile of dexamethasone and tobramycin from the test and RS products. A prospective applicant may use the same method or different methods for IVRT of dexamethasone and tobramycin.

   Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method.

Comparative characterization studies:

Comparative physicochemical characterization of the test product and RS product. The comparative study should be performed on at least three batches of both the test product[4] and RS product and should include:

a. Appearance.
b. Specific gravity.
c. Acidity and alkalinity of the extracted ointment base.
d. Crystallinity and crystal habit of dexamethasone.
e. Particle size and size distribution of dexamethasone.
f. Particle size and size distribution of tobramycin.
g. Rheological properties including yield stress and viscosity. Viscosity should be characterized over a range of shear rates.

II. Option 2: One in vitro bioequivalence study and one in vivo bioequivalence study with pharmacokinetic endpoints

One in vitro bioequivalence study:

1. Type of study: In vitro drug release testing of tobramycin
   Design: Should be performed on three batches of both test and RS products using at least 12 units from each batch
   Strength: 0.1%; 0.3%
   Additional comments: The IVRT method study should include information on the method development and validation to detect potential formulation differences and capture the complete release profile of tobramycin from the test and RS products.

   Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method.

[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, crossover or parallel design in vivo in aqueous humor
   Strength: 0.1%; 0.3%
   Subjects: Patients undergoing indicated cataract surgery
   Additional comments: Specific recommendations are provided below.

Analyte to measure: Dexamethasone in aqueous humor

Bioequivalence based on (90% CI): Dexamethasone

Additional comments regarding the in vivo pharmacokinetic study in aqueous humor:

1. The study should be conducted in patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery. A single dose of the test or reference product is instilled into the inferior cul-de-sac of the eye prior to cataract extraction. Only one single sample of aqueous humor is collected from one eye of each patient, at one assigned sampling time point.

   Applicant may consider a parallel design for the bioequivalence study. If using a parallel study design, please note that each patient should receive only one treatment, test or reference, but not both. Alternatively, a crossover study design may be used in patients undergoing indicated cataract surgery for both eyes. When a crossover study design is used, each patient should receive both test and reference treatments. The wash-out period for the crossover study should not exceed 35 days.

2. To demonstrate bioequivalence, an adequate estimation of the rate (C_{max}) and extent (AUC) of dexamethasone absorption is needed. The following statistical model is recommended:

   The mean AUC_t for each product and time point *t* of measurement is calculated by using the mean concentrations ($\overline{C_t}$) at each time point *t* to derive the mean profile for each product. On the basis of the trapezoid rule, mean AUC_t is computed as the weighted linear combination of these mean concentrations at each time point through time *t*. The AUC_t is the area under the concentration-time curve from zero to the time *t*. Generally, we have *j* concentration measurements at times $t_1 < t_2 < t_3 \ldots, < t_j$ ($t_1 > 0$).

   AUC_{t_j} is calculated for time from 0 to t_j as:

$$AUC_{t_j} = t_1 \times \overline{C_{t_1}} / 2 + \sum_{i=1}^{j-1} \left(\overline{C_{t_i}} + \overline{C_{t_{i+1}}}\right) \times (t_{i+1} - t_i) / 2$$

The ratio (R_t) of AUC_t from the test product to AUC_t from the reference product is used to assess bioequivalence for each time *t* of interest. Estimation of the standard deviation(s) of R_t may be done via the bootstrapping technique or a parametric method.

Bioequivalence is supported if the 90% confidence interval for R_t ($R_t \pm 1.645\ s_t$) lies within (0.80, 1.25). The bootstrapping technique or a parametric method can be used to determine C_{max} and T_{max} and assess bioequivalence for C_{max}.

3. A protocol may be submitted to the Division of Bioequivalence for review and comment prior to conducting the study. The study design and statistical analysis plan should be specified a *priori* in the protocol. All details of the computations, including computation code, should be submitted.

4. Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentrations as the RLD. For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulation for abbreviated new drug applications, 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Document History: Recommended June 2012; Revised November 2012, June 2013, June 2016, February 2024

Unique Agency Identifier: PSG_050616