Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Dexamethasone; Neomycin Sulfate; Polymyxin B Sulfate

February 2024

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Active Ingredients:	Dexamethasone; Neomycin sulfate; Polymyxin B sulfate
Dosage Form:	Suspension/drops
Route:	Ophthalmic
Strength:	0.1%; EQ 3.5 mg Base/mL; 10,000 units/mL
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive comparative characterization studies, or (2) one in vivo bioequivalence study

I. Option 1: Two in vitro bioequivalence studies with supportive comparative characterization 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.*

Two in vitro bioequivalence studies:

1. Type of study: Drug particle size and particle size distribution of dexamethasone
   Design: In vitro bioequivalence study on three batches of both test and reference standard (RS) products
   Strength: 0.1%; EQ 3.5 mg Base/mL; 10,000 units/mL
   Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles. Prospective applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Full particle size distribution profiles representative of all test product and RS product batches tested should be submitted as supporting information.

   Parameters to measure: D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$

   Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) analysis of the D_{50} and SPAN. Prospective applicants should provide no less than 10 datasets from three batches each of the test and RS products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

2. Type of study: Comparative in vitro release testing (IVRT) of dexamethasone
   Design: Should be performed on three batches of both test and RS products using at least 12 units from each batch
   Strength: 0.1%; EQ 3.5 mg Base/mL; 10,000 units/mL
   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.

   Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]

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. Crystalline habit of dexamethasone
b. Appearance
c. pH
d. Specific gravity
e. Osmolality
f. Surface tension
g. Viscosity
h. Soluble fraction of dexamethasone in the final drug product

II. Option 2: One in vivo bioequivalence study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, crossover or parallel design, in vivo in aqueous humor
   Strength: 0.1%; EQ 3.5 mg Base/mL; 10,000 units/mL
   Subjects: Patients undergoing indicated cataract surgery

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 from 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 crossover study design is used, each patient should receive both of test and reference treatments. The wash-out period for the crossover study should not exceed 35 days.

2. In order to demonstrate bioequivalence, an adequate estimation of the rate (C_{max}) and extent (AUC) of dexamethasone absorption is needed.

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

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 $t_1 < t_2 < t_3 .., < t_j$ ($t_1 > 0$).

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

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

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. 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 in the application.

4. Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentration 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) regulations for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the applicant should identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Additional information:

Device:
The RLD is presented in a bottle with a dropper tip. The bottle with dropper tip is the device constituent part.

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 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*.[b]

Quality assessment:
For quality-related recommendations for supporting drug product development, refer to the most recent version of the FDA guidance for industry on *Quality Considerations for Topical Ophthalmic Drug Products*.[b]

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.