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Draft – Not for Implementation

Draft Guidance on Dexamethasone; Neomycin Sulfate; Polymyxin B Sulfate

November 2024

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Active Ingredients:	Dexamethasone; Neomycin sulfate; Polymyxin B sulfate
Dosage Form:	Ointment
Route:	Ophthalmic
Strength:	0.1%; EQ 3.5 mg Base/gm; 10,000 units/gm
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 (T) 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 T 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 T 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 bioequivalence 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, neomycin sulfate, and polymyxin B sulfate
   Design: Should be performed on three batches of both T and reference standard (RS) products using at least 12 units from each batch
   Strength: 0.1%; EQ 3.5 mg base/gm; 10,000 units/gm
   Additional comments: The IVRT method(s) study should be developed and validated to show the reproducibility and discriminatory power. Data demonstrating discriminating ability of the IVRT method(s) to detect potential differences in formulation and/or manufacturing parameters (e.g., drug loading, ointment base with varied viscosity[4]) should be provided in the development and validation report in abbreviated new drug application (ANDA) submission. A prospective applicant may use the same method or different methods for IVRT of dexamethasone, neomycin sulfate, and polymyxin B sulfate.

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

Comparative characterization studies:

The comparative studies should be performed on at least three batches of both the T product [5] and the 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. 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: IVRT of neomycin sulfate and polymyxin B sulfate
   Design: Should be performed on three batches of both T and RS products using at least 12 units from each batch
   Strength: 0.1%; EQ 3.5 mg base/gm;10,000 units/gm

[4] Bao, Q., Shen, J., Jog, R., Zhang, C., Newman, B., Wang, Y., Choi, S., & Burgess, D. J. (2017). In vitro release testing method development for ophthalmic ointments. International Journal of Pharmaceutics, 526(1), 145–156. https://doi.org/10.1016/j.ijpharm.2017.04.075

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

Additional comments: The IVRT method(s) study should be developed and validated to show the reproducibility and discriminatory power. Data demonstrating discriminating ability of the IVRT method(s) to detect potential differences in formulation and/or manufacturing parameters (e.g., drug loading, ointment base with varied viscosity) should be provided in the development and validation report in ANDA submission. A prospective applicant may use the same method or different methods for IVRT of neomycin sulfate and polymyxin B sulfate.

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

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%; EQ 3.5 mg base/gm; 10,000 units/gm
   Subjects: Patients undergoing indicated cataract surgery
   Additional comment: 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 T or RS 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, T or RS, 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 T and RS. 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 T product to AUC_t from the RS 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. Questions regarding any protocols may be submitted to FDA prior to conducting the study.

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.

Additional comment:

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*.[a]

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.