

## Draft Guidance on Dexamethasone; Neomycin Sulfate; Polymyxin B Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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| <b>Active Ingredients:</b>  | Dexamethasone; Neomycin sulfate; Polymyxin B sulfate |
| <b>Dosage Form; Route:</b>  | Suspension/drops; ophthalmic                         |
| <b>Strength:</b>            | 0.1%; EQ 3.5 mg base/mL; 10,000 units/mL             |
| <b>Recommended Studies:</b> | Two options  |

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### I. Option One: In vitro Studies

To qualify for the in vitro option for this drug product all of the following criteria should be met:

- i. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)<sup>1</sup> and quantitatively (Q2)<sup>2</sup> the same (Q1/Q2).<sup>3</sup>
- ii. Acceptable comparative physicochemical characterization 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 should include:<sup>4</sup>
  - Polymorphic form of dexamethasone
  - Appearance, pH, specific gravity, osmolality, surface tension, and viscosity as a function of applied shear.
  - Soluble fraction of dexamethasone in the final drug product
  - Drug particle size distribution. The particle size distribution should be compared using PBE (95% upper confidence bound) based on D<sub>50</sub> and SPAN [i.e. (D<sub>90</sub>-D<sub>10</sub>)/D<sub>50</sub>]. The applicant should provide no fewer than ten data sets from three different batches of both the test and reference products for PBE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.

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<sup>1</sup> Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

<sup>2</sup> Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

<sup>3</sup> 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*.

<sup>4</sup> The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

- iii. Acceptable comparative in vitro drug release of dexamethasone from the test and RS formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.
  - iv. Acceptable comparative in vitro antimicrobial kill rates of the test and RS formulations (Specific recommendations are provided below)
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## **I. Option Two: In vivo and In vitro studies**

- 1. Type of study: Bioequivalence study with pharmacokinetic (PK) 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

Additional Comments: Specific recommendations are provided below.

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- 2. Type of study: In vitro bioequivalence study  
Design: In vitro microbial kill rate study  
Strength: 0.1%; EQ 3.5 mg base/mL; 10,000 units/mL  
Subjects: Not applicable

Additional Comments: Specific recommendations are provided below.

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**In vivo pharmacokinetic study in aqueous humor:** This study should be conducted in order to evaluate the steroid component (dexamethasone) of the combination product.

**Analytes to measure (in appropriate biological fluid):** Dexamethasone in aqueous humor

**Bioequivalence based on (90% CI):** Dexamethasone

### **Additional Comments Regarding the In Vivo Pharmacokinetic Study in Aqueous Humor:**

- 1. The study is 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 (Cmax) 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  $t_1 < t_2 < t_3 \dots, < t_j$  ( $t_1 > 0$ ).

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

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

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 (0.8, 1.25). The bootstrapping technique or a parametric method can be used to determine Cmax and Tmax and assess bioequivalence for Cmax.

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 Reference Listed Drug (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.

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### **Additional Comments Regarding the In Vitro Microbial Kill Rate Study:**

1. An In Vitro Microbial Kill Rate Study should be conducted in order to evaluate the antibiotic portion (neomycin sulfate; polymyxin b sulfate) of the combination product. The study should compare the antimicrobial activity of neomycin sulfate; polymyxin b sulfate in the test and RS product against the following:
  - All organisms listed in the USP Preservative Effectiveness Test
  - All organisms listed in the “Indications” section of the RLD product labelingThe in vitro microbial kill rate study should be conducted by using at least 12 replicates for each kill rate study of each organism to demonstrate bioequivalence (BE) between the test and reference products.
  
2. The test and reference formulations, along with a negative control, should be compared in vitro for bacterial kill rates. Each product should be challenged with approximately  $5 \times 10^4$  cfu/mL of each of the organisms listed in the USP Antimicrobial Effectiveness Test and in the reference product labeling. The population for each test organism/product for designated time intervals (i.e., 5, 15, 30, 60 and 120 minutes) should be determined by counting surviving colonies after incubation. Kill rates should be determined for each product and equivalence declared if both the test and reference products produce the same in vitro kill rates on all organisms tested. The following are additional recommendations regarding the study design:
  - a. The solution in which the testing for activity of the antibacterial agent in the test product is done should mimic as closely as possible the lacrimal fluid of the eye in composition, molarity, pH, etc.
  - b. The testing procedure should include some way for the antimicrobial agent to be inactivated at the time samples are withdrawn to perform colony counts for surviving organisms (e.g. filtration, dilution, chemical).
  - c. The time at which samples are withdrawn to determine organism survival should be: 0, 7.5, 15, 30 and 60 minutes. The two one-sided test procedure is recommended to determine the 90% confidence interval for the test/reference ratios of average kill rate for each sampling time point.
  - d. The organisms to be tested are those listed in USP <51> Antimicrobial Effectiveness Testing and organisms to be listed in the package insert for the product.
  - e. The final inoculum concentration of bacteria, yeast or spores that are tested should be at least  $5 \times 10^5$  CFU/mL.
  - f. Media used to determine the organism survival should be appropriate to allow for recovery of surviving organisms.
  - g. The temperature at which organism recovery media are incubated should be the temperature of the eye.
  - h. All recovery media should be incubated for the appropriate amount of time to allow for the growth of the organism for which recovery is being attempted.
  - i. Recovery of organism testing should be done in triplicate at each dilution of test material.
  - j. The method of determining the colony counts of organism on survival media should be described in the protocol (e.g. counted under magnification).
  - k. The test methodology will need to be validated prior to using it to determine activity of the product against the organisms. It is suggested that at the time a test method is being written that a validation protocol be written.

**In vitro dissolution test method and sampling times:** Please develop an in vitro drug release testing method for this drug product for stability and quality controls. Specifications will be determined upon review of the data submitted in the application.