

Draft Guidance on Dexamethasone; Tobramycin

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Active Ingredient: Dexamethasone; Tobramycin

Dosage Form; Route: Suspension; ophthalmic

Recommended Study: Two options

I. Option One: In vitro studies

To qualify for the in vitro option for this drug product (dexamethasone; tobramycin 0.05%; 0.3%), all of the following criteria should be met:

- i. The test and reference listed drug (RLD) formulations are qualitatively¹ and quantitatively² the same (Q1/Q2).
- ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The characterization study should be performed on at least three exhibit batches of both the test and RLD products³ and should include:
 - Comparative crystalline habit of dexamethasone
 - Comparative appearance, pH, specific gravity, osmolality, surface tension, buffer capacity, and viscosity as a function of applied shear (Viscosity measurement should be conducted in the presence and absence of tear fluid.)
 - Comparative re-dispersibility (time required to re-disperse the formulation, and sedimentation time)
 - Comparative soluble fraction of dexamethasone in the final drug product
 - Comparative unit dose content (one drop per unit dose, for both APIs) (Provide data for the amount of unit dose (one drop) with assay for both APIs from a minimum of ten units from three batches each of the test and reference products. The unit dose content should be compared using population BE (95% upper confidence bound).)
 - Comparative drug particle size distribution (The particle size distribution should be compared using population BE (95% upper confidence bound) based on D50 and SPAN. The applicant should provide no fewer than ten data sets from three different batches each of the test and reference products for the population BE

¹ Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

² Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the reference product.

³ All three exhibit batches should be at least 1/10 the size of the commercial batch, and the manufacturing process used for the three exhibit batches should be reflective of the process used for the commercial batch.

analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.)

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

- 1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
Design: Single-dose, crossover or parallel design in vivo in aqueous humor
Strength: 0.05% / 0.3%
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: 0.05% / 0.3%
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 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. 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 abbreviated new drug application (ANDA).
4. Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentrations 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) regulation for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], 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.
5. Changes in any of the inactive ingredients can change the safety and efficacy of an ophthalmic drug product. Therefore, an applicant may need to also conduct an in vivo BE

study with clinical endpoints for any dexamethasone and tobramycin ophthalmic suspension that has a different inactive ingredient or a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD.

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 (tobramycin) of the combination product. The study should compare the antimicrobial activity of tobramycin in the test and reference product against the following:

- All organisms listed in the USP Preservative Effectiveness Test
- All organisms listed in the “Indications” section of the reference product labeling

The antimicrobial activity of tobramycin in the test and reference products should be compared in the in vitro BE study, at a minimum, against the following 17 organisms: *Candida albicans*, *Aspergillus niger*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, *Proteus vulgaris*, *Haemophilus influenzae*, *Haemophilus aegyptius*, *Moraxella lacunata*, *Acinetobacter calcoaceticus*, *Neisseria perflava* OR *Neisseria sicca*.

The 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 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 5×10^4 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 times 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 5×10^5 CFU/mL.
- f. Media used to determine 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 colony counts of the 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, a validation protocol also 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.