

Draft Guidance on Hydrocortisone; Neomycin Sulfate; Polymyxin B Sulfate

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic hydrocortisone; neomycin sulfate; polymyxin b sulfate.

Active Ingredient:	Hydrocortisone; Neomycin sulfate; Polymyxin b sulfate
Dosage Form; Route:	Suspension/drops; otic
Strength:	1%; EQ 3.5mg Base/mL; 10,000 Units/mL
Recommended Studies:	Two options: (1) Three in vitro bioequivalence studies with supportive physicochemical characterization studies or (2) one in vivo bioequivalence study with clinical endpoints

I. Option 1: Three in vitro bioequivalence studies with supportive physicochemical characterization studies

To qualify for the in vitro bioequivalence studies recommended in this guidance, all of the following criteria should be met:

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)¹ and quantitatively (Q2)² the same (Q1/Q2).
2. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) products. The study should be performed on at least three batches of both the test and RS products and should include:³
 - a. Crystalline habit of hydrocortisone
 - b. Appearance, pH, specific gravity, osmolality, surface tension, and viscosity as function of applied shear rates
 - c. Soluble fraction of hydrocortisone in the final drug product

Three in vitro bioequivalence studies:

1. Type of study: Comparative drug particle and particle size distribution of hydrocortisone
Additional Comments: The particle size distribution should be compared using PBE (95% upper confidence bound) based on D₅₀ and SPAN [i.e. (D₉₀-D₁₀)/D₅₀]. 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. Refer to the most recent version of the FDA product-specific guidance on *Budesonide inhalation suspension*^a for additional information regarding PBE.
2. Type of study: Comparative in vitro drug release testing of hydrocortisone
Additional comments: Detailed information on development and validation of a proposed in vitro drug release testing method should be provided. The methodology should be able to discriminate the effect of formulation and/or process variability in the production of the test formulation.
3. Type of study: Comparative in vitro antimicrobial kill rates of the test and RS formulations.
Additional Comments: Refer to the most recent version of the FDA product-specific guidance on *Guidance on Dexamethasone, Neomycin and polymyxin B sulfates ophthalmic suspension*^a for additional comments regarding the in vitro antimicrobial kill study design.

II. Option 2: One in vivo bioequivalence study with clinical endpoints

In vivo bioequivalence studies with clinical endpoint are requested for any generic hydrocortisone; neomycin sulfate; polymyxin b sulfate otic suspension/drops product that has differences in inactive ingredient compared to the RLD, or unacceptable data from in vitro comparative studies

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 concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product

³ The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

1. Type of study: Bioequivalence study with clinical endpoints
Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
Subjects: Males and females (non-pregnant) with superficial bacterial infections of the external auditory canal

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of neomycin and polymyxin B sulfates, comparing the test product versus the RLD and vehicle (placebo) control, each administered as four drops instilled into the affected ear thrice daily for seven days (1 week). Prior to administration, the suspension should be warmed by holding the bottle in the hand for one to two minutes and shaken well immediately before using. The subject should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. In the event of bilateral otitis externa, both ears should be treated. However, the ear with the more severe signs and symptoms at baseline, designated as the “study ear”, will be used for the evaluations throughout the course of the study. The two co-primary endpoints are clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) and time to end of pain. Both determined at the test of cure visit on study day 14-21 (i.e., 7-14 days after the end of treatment).
2. A placebo (vehicle) control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
3. Inclusion criteria (the sponsor may add additional criteria):
 - a. Male or non-pregnant female aged 18 to 65 years.
 - b. Clinical diagnosis of bacterial otitis externa with signs and symptoms of otalgia, edema and tenderness.
 - c. Culture-based diagnosis of acute bacterial otitis externa (i.e., positive baseline bacterial culture for the presence of *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella- Enterobacter species*, *Neisseria species*, and *Pseudomonas aeruginosa*). As the results of the baseline bacterial culture may not be known until after the subject has completed treatment, subjects who meet all the other inclusion/exclusion criteria may be enrolled in the study pending the results of the bacterial culture. A baseline bacterial culture negative for *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella- Enterobacter species*, *Neisseria species*, and *Pseudomonas aeruginosa* will exclude the subject from the Per Protocol (PP) and modified intent-to-treat (mITT) analyses.
4. Exclusion criteria (the sponsor may add additional criteria):
 - a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period.

- b. Current diagnosis or history of tympanic membrane perforation or damage or tympanostomy tubes.
 - c. Current diagnosis or history of diabetes mellitus, psoriasis, otitis media, malignant otitis externa, mastoid cavities, stenosis, exostosis or tumors of either ear.
 - d. Current diagnosis of fungal or viral infection of either ear.
 - e. Current diagnosis of dermatitis of the affected ear or surrounding area.
 - f. Current presence of any other infection of the ears or other medical condition that might adversely impact the safety of the study participants or confound the study results.
 - g. Known hypersensitivity to neomycin, kanamycin, paromomycin, streptomycin, gentamicin, polymyxin B sulfates, hydrocortisone or any component of the test or RLD.
 - h. Use of any systemic antibacterial within four weeks prior to baseline.
 - i. Use of any topical medication in the affected ear within two weeks prior to baseline.
5. The protocol should include a list of the prescription and non-prescription/over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Otic product administered to either ear, other than the assigned study product.
 - b. Topical or systemic antibiotics, other than the assigned study product.
 - c. Topical or systemic corticosteroids, other than the assigned study product.
 - d. Systemic or topical immunosuppressive drugs or immunomodulators (e.g., azathioprine, infliximab, calcineurin inhibitors).
 - e. Assigned study product should not be used if the tympanic membrane is perforated or in the presence of viral infections of the external canal, including herpes simplex, vaccinia and varicella infections.
 - f. Subjects should be instructed to not use the assigned study product in the eyes, to avoid contaminating the bottle tip with material from the ear, fingers, or other source, and to discontinue study product at the first appearance of a skin rash or any other sign of hypersensitivity or an allergic reaction.
6. Subjects who do not respond to therapy after 48 hours will receive standard therapy (i.e., early escape clause). Patients need close clinical observation on neomycin-associated sensorineural hearing loss.
7. The two co-primary endpoints are the proportion of subjects in the PP population with clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) of the study ear and time to end of pain for the study ear. The two co-primary endpoints are to be evaluated at the test of cure visit on study day 14 to 21 (7 to 14 days after the end of treatment). If both ears of the subject are infected, the ear with the more severe signs and symptoms at baseline should be designated as the study ear and evaluated at each study visit (i.e., Baseline visit, end of treatment visit, and test of cure visit).

8. During each study visit, score each of the following signs and symptoms using the following scale:
 - a. Signs: edema, erythema, and otorrhea
 - b. Symptoms: otalgia and tenderness
 - c. Scoring Scale:

0	= none	(complete absence of any signs or symptoms)
1	= mild	(slight)
2	= moderate	(definitely present)
3	= severe	(marked, intense)

9. Time to end of pain for the affected ear should be evaluated at each post-baseline evaluation visit [(i.e., at the end of treatment visit (study day 8-10) and the test of cure visit (study day 14-21)]. Throughout the study, subjects should record pain severity at least twice daily (prior to dosing) on a visual analog scale of 0 to 15, where 0 = no pain and 15 = severe pain. Each subject should record the time and date at which the study ear pain ended. The time to end of pain is the interval (in hours) between the first dose of study drug and the time when the study ear pain ended. If study ear pain continued to the end of the study, the value of the time to end of pain variable is set to the length of time between the time of the first dose of study drug and the last time point when a pain measurement was recorded. If the “time to end of ear pain” field is blank, then it should be considered that the pain did not end for the subject while the subject was under observation and the value of the time to end of pain variable is set to the length of time between the time of the first dose of study drug and the last time point when a pain measurement was recorded.

10. Post-therapy cultures are necessary only if the subject’s clinical response is unsatisfactory. Routine post-therapy cultures frequently yield positive results due to the presence of normal flora or other colonization after treatment. If the use of an ear wick or debridement of the ear is permitted during the study, the use of these procedures should be comparable among treatment groups.

11. Subjects with a negative culture at baseline should be discontinued from the study and excluded from the mITT and PP populations, but included in the safety population.

12. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
 - a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of actual treatment (exposure): test product, RLD, placebo
 - i. Duration of treatment (total exposure in days)
 - j. Completed the study (yes/no)

- k. Reason for premature discontinuation of subject
 - l. Subject required additional treatment for acute otitis externa due to unsatisfactory treatment response (yes/no)
 - m. PP population inclusion (yes/no)
 - n. Reason for exclusion from PP population
 - o. Modified Intent to Treat (mITT) population inclusion (yes/no)
 - p. Reason for exclusion from mITT population
 - q. Safety population inclusion (yes/no)
 - r. Reason for exclusion from safety population
 - s. Baseline edema score
 - t. Baseline otalgia score
 - u. Baseline tenderness score
 - v. Final designation as clinical cure (yes/no)
 - w. Pain relief achieved while on study (yes/no)
 - x. If pain relief achieved, time to relief of pain (hours)
 - y. Treatment compliance: number of missed doses per subject
 - z. Concomitant medication (yes/no)
 - aa. Adverse event(s) reported (yes/no)
13. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Name of actual treatment (exposure): test product, RLD, placebo control
 - d. Visit number
 - e. Visit date
 - f. Number of days since baseline visit
 - g. Evaluator: identity of evaluator
 - h. Edema score
 - i. Erythema score
 - j. Otorrhea score
 - k. Oalgia score
 - l. Tenderness score
 - m. Composite (total) signs and symptoms score
 - n. Culture result
 - o. Concomitant medication reported during this visit (yes/no)
 - p. Adverse event reported during this visit (yes/no)
 - q. Laboratory testing during this visit (yes/no)
14. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)^a for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
15. Refer to the study data standards resources, <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

Waiver request of in vivo testing: Not applicable.

Additional information:

Device:

The reference listed drug (RLD) product is presented in a bottle fitted with a dropper tip. The bottle with dropper tip is the device constituent.

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

Unique Agency Identifier: PSG_060613

^a For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>

^b For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.