

Draft Guidance on Finafloxacin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Finafloxacin

Dosage Form; Route: Suspension/drops; otic

Recommended Studies: Two options: in vitro or in vivo study

I. In Vitro Option:

To qualify for the in vitro option for this drug product, 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.
 2. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) products. The comparative studies should be performed on at least three batches of both the test and RS products and should include:³
 - Polymorphic form of finafloxacin
 - Crystalline shape and morphology of finafloxacin
 - Appearance, pH, specific gravity, osmolarity, and viscosity
 - Soluble fraction of finafloxacin in the final drug product
 - Drug particle size distribution. 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.
 3. Acceptable comparative in vitro drug release tests of finafloxacin 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.
-

II. In Vivo Option

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.

An in vivo bioequivalence (BE) study with clinical endpoints is recommended for any generic finafloxacin otic suspension 0.3% that is not Q1/Q2 to the RLD, or has differences in comparative physicochemical characterization data greater than described in the in vitro option above.

Number of Studies: One study
Type of study: BE study with clinical endpoint
Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
Strength: 0.3%
Subjects: Adult males and nonpregnant females with acute otitis externa

Additional comments: Specific recommendations are provided below

Analytes to measure (in appropriate biological fluid): N/A

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: N/A

Additional comments regarding the BE study with clinical endpoint

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoint in the treatment of acute otitis externa comparing the test product versus RS and vehicle control, each administered as four drops instilled into the affected ear twice daily (about 12 hours apart, for example, at 8 a.m. and 8 p.m.) for seven days (1 week).
2. Prior to administration, the suspension should be warmed by holding the bottle in the hand for one or two minutes prior to dosing to avoid dizziness that may result from instillation of a cold suspension. Shake bottle well before use. The subject should lie with the affected ear upward then instill the drops and maintain that position for 60 seconds to facilitate penetration of drops into the ear canal.
3. In the event of bilateral acute 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 evaluations throughout the course of the study. If both ears have the same severity rating, then the “right” ear will be designated as the “study ear.”
4. The primary endpoint is clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) determined at the test of cure visit on study day 11-14 (i.e. 4-7 days after end of treatment).

5. A placebo control arm is recommended to demonstrate that the test product and RS are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
6. OGD has evaluated the need for a placebo arm in BE studies for this indication. Because some proportion of enrolled subjects will have spontaneous resolution of otitis externa, OGD recommends a placebo-controlled study with an early-escape clause stating that subjects who do not respond to therapy after 48 hours will receive standard therapy. We believe that a placebo-controlled trial is ethically acceptable, with the inclusion of an escape clause. In addition, by limiting the study population to adults who can consent to their own participation, the risk of subjecting young children to harmful side effects or to prolonged pain will be avoided.
7. Inclusion criteria (the sponsor may add additional criteria):
 - Males or nonpregnant females, 18-65 years of age
 - Clinical diagnosis of acute bacterial otitis externa with signs and symptoms of otalgia, edema, and tenderness
 - Culture-based diagnosis of acute bacterial otitis externa (i.e., positive baseline bacterial culture for the presence of *Pseudomonas aeruginosa* or *Staphylococcus aureus*). As the results of the baseline bacterial culture may not be known until after the subject has completed treatment, subjects who meet all other inclusion/exclusion criteria may be enrolled in the study pending results of the bacterial culture. A baseline bacterial culture negative for *Pseudomonas aeruginosa* and *Staphylococcus aureus* will exclude the subject from per-protocol (PP) and modified intent-to-treat (mITT) analyses.
8. Exclusion criteria (the sponsor may add additional criteria):
 - Females who are pregnant, breast feeding, or who wish to become pregnant during the study period
 - Signs and symptoms of current episode of otitis externa began more than 21 days (3 weeks) prior to baseline
 - Current diagnosis or history of tympanic membrane perforation or damage or tympanostomy tubes
 - Current diagnosis or history of diabetes mellitus, psoriasis, immunocompromise, autoimmune conditions, otitis media, malignant otitis externa, mastoid cavities, stenosis, exostosis, or tumors of either ear
 - Current diagnosis of fungal infection of either ear
 - Current diagnosis of viral infections of the external ear or ear canal, including varicella and herpes simplex infections
 - Current diagnosis of dermatitis of the affected ear or surrounding area
 - Current presence of any other infection of the ears or other medical condition that might adversely impact the safety of study participants or confound study results
 - Known hypersensitivity to fluroxacin, any member of the quinolone class of antimicrobial agents, or any component of test or RLD products
 - Use of any systemic antibacterial within four weeks prior to baseline
 - Use of any ototopical medication in the affected ear within two weeks prior to baseline

9. The protocol should include a list of the prescription and nonprescription/over-the-counter (OTC) drug products, procedures, and activities that are prohibited during the study, such as:
- Otic product administered to either ear, other than the assigned study product;
 - Otological or systemic antibiotics, other than the assigned study product;
 - Otological or systemic corticosteroids, other than the assigned study product;
 - Systemic or otological immunosuppressive drugs or immunomodulators (e.g., azathioprine, infliximab, calcineurin inhibitors).

10. During each study visit (e.g., baseline, end of therapy, test of cure) assess the affected ear(s) by scoring each of the following signs and symptoms using the following scale:

Signs: edema, erythema, and otorrhea

Symptoms: otalgia and tenderness

Scoring Scale:

0	None	Complete absence of any signs or symptoms
1	Mild	Slight
2	Moderate	Definitely present
3	Severe	Marked, intense

11. 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.

12. The protocol should clearly define per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
- a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
 - i. Meet all inclusion/exclusion criteria
 - ii. Are dosed a pre-specified proportion of the scheduled doses (e.g., at least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., using subject diaries).
 - iii. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
 - iv. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
 - b. The mITT population includes all randomized subjects who use at least one dose of product and have a positive bacterial culture in the study ear at baseline.
 - c. The safety population include all randomized subjects who use at least one dose of product

13. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population as treatment failures. Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population

analyses as treatment failures, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF). Applicants should provide a pre-specified definition of lack of treatment effect.

14. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
15. If the study allows for the use of a rescue medication, the Applicant should submit a data set that includes daily rescue medication use for each individual who used the rescue medication at any point during the study. The Applicant should pre-specify rescue medication use (type, amount, frequency, reason to use), maximum daily rescue medication use, and any limitations (e.g., cannot use rescue medication within pre-specified number of hours prior to primary endpoint evaluation) for rescue medication use during the study.
16. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.
17. All pregnancies should be reported, including outcome information.
18. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 2 months and older).
19. The method of randomization should be described in the protocol and the randomization schedule should be provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study to minimize bias. The Applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
20. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference, and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

21. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.
22. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
23. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_0: \pi_T - \pi_R < \Delta_1 \text{ or } \pi_T - \pi_R > \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$$

where π_T = the success rate of the primary endpoint for the treatment group, and
 π_R = the success rate of the primary endpoint for the reference group.

The null hypothesis, H_0 , is rejected with a type I error rate (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\Delta_1 = -0.20$ and $\Delta_2 = 0.20$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_0: \mu_T / \mu_R < \theta_1 \text{ or } \mu_T / \mu_R > \theta_2 \text{ versus } H_A: \theta_1 \leq \mu_T / \mu_R \leq \theta_2$$

where μ_T = mean of the primary endpoint for the test group, and
 μ_R = mean of the primary endpoint for the reference group

The null hypothesis, H_0 , is rejected with a type I error rate (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products (μ_T / μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

24. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error rate (α) of 0.05, using the mITT population.

25. The study data should be submitted in standardized format. Please refer to study data standards published at www.FDA.gov.⁴
26. The protocol should include a detailed statistical analysis plan.
27. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
- a. Study identifier
 - b. Unique subject identifier
 - c. Subject identifier for the study
 - d. Study site identifier: study center
 - e. Age
 - f. Age units (years)
 - g. Sex
 - h. Race
 - i. Description of planned arm
 - j. Description of actual arm
 - k. Planned treatment (character)
 - l. Planned treatment (number)
 - m. Actual treatment (character)
 - n. Actual treatment (number)
 - o. Safety population flag (yes/no)
 - p. Reason for exclusion from safety population
 - q. Intent-to-treat population flag (yes/no)
 - r. Modified intent to treat (mITT) population flag (yes/no)
 - s. Reason for exclusion from mITT population
 - t. PP population flag (yes/no)
 - u. Reason for exclusion from PP population
 - v. Completers population flag (yes/no)
 - w. Baseline culture positive (yes/no)
 - x. Randomized population flag (yes/no)
 - y. Date of randomization
 - z. Date of enrollment
 - aa. Duration of current episode
 - bb. Treated ear (right/left/both)
 - cc. Study ear (right/left)
 - dd. Date/time of first exposure to treatment
 - ee. Date/time of last exposure to treatment
 - ff. Duration of treatment (total exposure in days)
 - gg. End of study date
 - hh. End of study status
 - ii. End of treatment status
 - jj. Subject required additional treatment for acute otitis externa due to unsatisfactory treatment response (yes/no)

⁴ Study Data Standards for Submission to CDER available at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

- kk. Date of rescue treatment
- ll. Compliance rate (%)
- mm. Treatment compliance: number of missed doses per subject
- nn. Concomitant medication (yes/no)
- oo. Baseline edema score
- pp. Baseline otalgia score
- qq. Baseline tenderness score
- rr. Final designation as clinical cure (yes/no)
- ss. Pain relief achieved while on study (yes/no)
- tt. If pain relief achieved while on study, time to relief of pain (days)
- uu. Adverse event(s) reported (yes/no)
- vv. Censoring status (1/0)
- ww. Reason for discontinuation from study (character)
- xx. Reason spec for discontinuation from study (character, additional details regarding subject's discontinuation from study)
- yy. Reason for discontinuation from treatment (character)
- zz. Reason spec for discontinuation from treatment (character, additional details regarding subject's discontinuation from treatment)
- aaa. Evaluator initial (character)

28. Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis time point, using the following headings, if applicable:

- a. Study identifier
- b. Unique subject identifier
- c. Subject identifier for the study
- d. Study site identifier
- e. Age
- f. Age unit (years)
- g. Sex
- h. Race
- i. Safety population flag (yes/no)
- j. ITT population flag (yes/no)
- k. mITT population flag (yes/no)
- l. PP population flag (yes/no)
- m. Description of planned treatment
- n. Description of actual treatment
- o. Planned treatment (character)
- p. Planned treatment (number)
- q. Actual treatment (character)
- r. Actual treatment (number)
- s. Completers population flag (yes/no)
- t. Visit number
- u. Visit date
- v. Number of days since baseline visit
- w. Evaluator: identity of evaluator
- x. Edema score

- y. Erythema score
- z. Otorrhea score
- aa. Otagia score
- bb. Tenderness score
- cc. Composite (total) signs and symptoms score
- dd. Culture result
- ee. Date/time of first exposure to treatment
- ff. Date/time of last exposure to treatment
- gg. Rescue treatment required (yes/no)
- hh. Date/time rescue treatment
- ii. Concomitant medication reported during this visit (yes/no)
- jj. Adverse event reported during this visit (yes/no)
- kk. Laboratory testing during this visit (yes/no)