This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Ointment; ophthalmic

**Recommended Studies:** Two options: (1) In vitro studies, or (2) in vivo clinical endpoint study

### Option I: In Vitro studies

To qualify for the in vitro option for ciprofloxacin hydrochloride ophthalmic ointment (EQ 0.3% base), all the following criteria must be met:

i. The test and Reference List Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) formulations. The comparative study should be performed on at least three exhibit batches of both test and reference products and should include:

   - Solid state form of ciprofloxacin hydrochloride
   - Appearance
   - Acidity and alkalinity of the extracted ointment base
   - Rheological properties including yield stress and viscosity. The applicant should characterize viscosity over a range of shear rates
   - Drug particle size and size distribution. Full profiles of the particle size distribution should also be submitted for all samples tested

iii. Acceptable comparative in vitro drug release rates of ciprofloxacin 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.

### Option II: In vivo clinical endpoint study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint
Design: Randomized, double-masked, parallel, placebo-controlled, in vivo
Strength: EQ 0.3% base
Subjects: Healthy males and nonpregnant females with bacterial conjunctivitis
Additional comments: Specific recommendations are provided below.

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Analytes to measure (in appropriate biological fluid): Not Applicable (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 endpoints in the treatment of bacterial conjunctivitis comparing the test product versus the reference listed drug (RLD) and placebo (vehicle) control, each administered as a ½ inch ribbon into the conjunctival sac three times a day on the first two days (Days 1 and 2), then two times a day for the next five days (Days 3 – 7). The recommended treatment duration is 7 days with office visits at Screening/Visit 1 (Day 0), Day 4 (± 1)/Visit 2 and Day 8 (± 1)/Visit 3. At each visit, perform best corrected visual acuity and slit lamp examination of the anterior segment of the eye for safety. Study treatment should stop at least 12 hours prior to obtaining bacterial culture of conjunctiva at Visit 3.

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. Healthy males or nonpregnant females aged at least 18 years with presumptive clinical diagnosis of bacterial conjunctivitis. Provide a clear definition of a clinical diagnosis of bacterial conjunctivitis, e.g., presence of bulbar injection (redness), ocular discharge, ocular discomfort and photophobia.
   b. Positive bacterial culture of conjunctiva obtained at Screening Visit (Day 0).
   c. Baseline best corrected visual acuity equivalent to 20/200 or better in each eye.

4. Exclusion Criteria (the sponsor may add additional criteria)
   a. Females who are pregnant, breast feeding or planning a pregnancy.
   b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
   c. Current clinically significant immunological deficiencies or neutropenia, HIV, HIV-positive, severe hepatic impairment, severe renal impairment, malignancies or uncontrolled diabetes mellitus.
   d. Symptoms of eye infection with onset of greater than 72 hours immediately prior to enrollment.
   e. Corneal ulcer.
   f. Chronic allergic conjunctivitis.
   g. Suspected fungal, viral or chlamydial eye infection.
h. Known hypersensitivity to ciprofloxacin or to any other components of the ciprofloxacin therapy.

i. Known hypersensitivity to other quinolones.

j. Use within two weeks prior to baseline of: 1) topical ophthalmic corticosteroid or 2) topical corticosteroid.

k. Use within four weeks prior to baseline of: 1) systemic corticosteroid or 2) local or systemic antimicrobial therapy.

l. Use within eight weeks prior to baseline of immunosuppressive medication for any indication.

m. Use within three months prior to baseline of: 1) radiation therapy or 2) anti-neoplastic agents.

n. Use within six months prior to baseline of: 1) ocular surgery (including ocular laser surgery), 2) significant eye trauma or 3) intravitreal or subtenon injection of ophthalmic corticosteroid.

o. Unwilling to refrain from wearing contact lenses.

5. Coadministration of routine, long-term ophthalmic medications for chronic ocular diseases (e.g., glaucoma) is permitted. When more than one topical ophthalmic medication is being used, the medicines must be administered at least one hour apart.

6. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:

   a. Topical, ophthalmic, inhaled or systemic corticosteroid.
   b. Intraocular corticosteroid implant.
   c. Intravitreal or subtenon injection of ophthalmic corticosteroid.
   d. Contact lenses.
   e. Ocular surgery.

7. The recommended co-primary endpoints are microbial eradication and clinical cure, based upon two clinical signs [bulbar injection (redness) and ocular discharge] and two clinical symptoms (ocular discomfort and photophobia).

8. Obtain culture of the affected conjunctiva at baseline and at least 12 hours after the last dose of study medication. Rate the microbial response as follows:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Eradication</td>
</tr>
<tr>
<td>1</td>
<td>Reduction</td>
</tr>
<tr>
<td>2</td>
<td>Persistence</td>
</tr>
<tr>
<td>3</td>
<td>Proliferation</td>
</tr>
</tbody>
</table>

These scores should be clearly defined to maintain consistency between investigator scoring at multiple sites. Define microbial cure as eradication (elimination of the presumed causative bacteria) with a score equal to zero. Refer to the Scale by Cagle et al. which displays published thresholds for the number of bacteria on a culture expected to be causative for bacterial conjunctivitis.1


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9. Two clinical signs [bulbar injection (redness) and ocular discharge] and two clinical symptoms (ocular discomfort and photophobia) should be evaluated at each visit and scored as follows:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
</tbody>
</table>

These scores should be clearly defined to maintain consistency between investigator scoring at multiple sites. Define clinical cure as the absence of any signs or symptoms (a score of zero for all four signs and symptoms).

10. The protocol should clearly define the 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. applied a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., by the use of subject diaries).
      iii. Do not miss a pre-specified number of the scheduled applications for more than one consecutive day.
      iv. Complete the evaluation within the designated visit window (+/- 1 day) with no protocol violations that would affect the treatment evaluation.
   b. The mITT and safety populations includes all randomized subjects who apply at least one dose of assigned product.

11. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward (LOCF). 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 using LOCF, 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 LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.

12. 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 note whether the medication was used prior to baseline visit, during the study, or both.

1871; 1 (5): 259-66. **NOTE**: Scale entitled “Table 2: Threshold Criteria for Culture Positive or Culture Negative Evaluation” is on pg. 261.
13. If the study allows for the use of a rescue medication, the Applicant should submit a data set that includes daily the date and time of each rescue medication use for each individual subject who used the rescue medication at any point during the study. The Applicant should pre-specify rescue medication use (name, type, amount, frequency, reason to use), maximum allowable amount of 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.

14. 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.

15. All pregnancies should be reported, including outcome information.

16. Generally, a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration 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) regulations for abbreviated new drug applications (ANDAs), 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. 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.

17. 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 in order 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.

18. A detailed description of the masking procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate masking 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.
19. 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 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 sponsor at any time.

20. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

21. To establish bioequivalence, it is recommended the following compound hypotheses be tested using the per protocol population for each of the two dichotomous primary endpoints (proportion of subjects with “clinical cure” at the Day 8/Visit 3 and proportion of subjects with “microbiological cure” at the Day 8/Visit 3):

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

where \( \pi_T = \) the success rate of the primary endpoint for the treatment group, and \( \pi_R = \) the success rate of the primary endpoint for the reference group.

The null hypothesis, \( H_0 \), is rejected with a type I error (\( \alpha \)) 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 both null hypotheses supports the conclusion of equivalence of the two products.

22. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference product should both be statistically superior to the placebo (vehicle). Conduct an appropriate inferential test with a type I error (\( \alpha \)) of 0.05, using the mITT population and each primary endpoint.

23. The study data should be submitted in standardized format. Please refer to study data standards published at www.FDA.gov.

24. The protocol should include a section with a fully detailed statistical analysis plan.

25. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:

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a. Study identifier
b. Unique 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 ocular inflammation due to unsatisfactory treatment response (yes/no)
m. Per Protocol (PP) population inclusion (yes/no)
n. Reason for exclusion from PP population
o. Modified Intent to Treat (mITT) Population (yes/no)
p. Reason for exclusion from mITT population
q. Safety population inclusion (yes/no)
r. Reason for exclusion from Safety population
s. Bulbous Injection (redness) Score at Day 0 (Screening/Visit1)
t. Discharge Score at Day 0 (Screening/Visit1)
u. Ocular Discomfort Score at Day 0 (Screening/Visit1)
v. Photophobia Score at Day 0 (Screening/Visit1)
w. Bulbous Injection (redness) Score at Day 4 ± 1 (Visit 2)
x. Discharge Score at Day 4 ± 1 (Visit 2)
y. Ocular Discomfort Score at Day 4 ± 1 (Visit 2)
z. Photophobia Score at Day 4 ± 1 (Visit 2)
aa. Bulbous Injection (redness) Score at Day 8 ± 1 (Visit 3)
bb. Discharge Score at Day 8 ± 1 (Visit 3)
c. Ocular Discomfort Score at Day 8 ± 1 (Visit 3)
dd. Photophobia Score at Day 8 ± 1 (Visit 3)
e. Clinical Cure at Day 8 ± 1 (Visit 3) (yes/no)
f. Bacteriologic Cure (Eradication) at Day 8 ± 1 (Visit 3) (yes/no)
gg. Treatment compliance: number of missed doses per subject
hh. Concomitant medication (yes/no)
ii. Adverse event(s) reported (yes/no)

26. Please 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. Unique subject identifier
c. Subject identifier for the study
d. Study site identifier (if applicable)
e. Name of planned treatment
f. Name of actual treatment
g. Safety population flag (yes/no)
h. Modified ITT population flag (yes/no)
i. Per-Protocol (PP) population flag (yes/no)
j. Analysis date
k. Analysis visit
l. Study visit within the designated window (yes/no)
m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
jj. Bulbous Injection (redness) Score
kk. Discharge Score
ll. Ocular Discomfort Score
mm. Photophobia Score
n. Additional treatment required during the visit (yes/no)
o. Adverse event reported during the visit (yes/no)
p. Concomitant medication during the visit (yes/no)