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Draft Guidance on Cyclosporine

August 2022

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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 cyclosporine.

Active Ingredient:	Cyclosporine
Dosage Form; Route:	Emulsion; ophthalmic
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive comparative characterization studies or (2) one in vivo bioequivalence study with clinical endpoints

I. Option 1: Two in vitro bioequivalence studies with supportive comparative characterization studies

To qualify for the in vitro option for this drug product, all 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).[3]

2. 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.[4]

Parameters to measure: Zeta potential, viscosity profile as a function of applied shear, pH, osmolality, surface tension and cyclosporine distribution in different phases within the formulation.

In vitro bioequivalence study 1:
Comparative globule size distribution of test and RS products

Additional comments: Dynamic light scattering method is recommended to measure the globule size distributions of test and RS formulations. Comparable globule size distribution profiles (intensity-based histograms) upon serial dilution should be provided. Non-ionic electrolyte-free dilution media are recommended. Information on the instrument, mode (if applicable), dilution medium and dilution level should be provided.

Bioequivalence based on (95% upper confidence bound): Equivalence between test and RS products with respect to globule size distribution should be demonstrated by a suitable method proposed by the sponsor. Population bioequivalence (PBE) based on D50 and SPAN (alternatively harmonic intensity weighted average particle diameter and polydispersity index derived from cumulant analysis of the intensity size distribution) for the globule size distribution only (the other parameters do not require PBE analysis). Applicants should provide no less than 10 datasets from 3 batches each of the Test and Reference products to be used in the PBE analysis. Please refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE.

In vitro bioequivalence study 2:
Acceptable comparative in vitro drug release study of cyclosporine from the test and RS products. The methodology used for in vitro drug release testing should be discriminative of process variabilities in the production of the test product.

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[1] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD 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 RLD product.
[3] 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*.
[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches. All 3 exhibit batches should be at least 1/10 the size of the commercial batch.

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

In vivo bioequivalence study with clinical endpoints is requested for any generic cyclosporine ophthalmic emulsion 0.1% that has differences in inactive ingredient than the RLD, or differences in acceptable formulation characteristics that cannot meet the criteria described in Option 1.

1. Type of study: Bioequivalence study with clinical endpoints
   Design: Randomized, double-blind, parallel, two-arm, in vivo
   Strength: 0.1%
   Subjects: Male and female children or adolescent patients with vernal keratoconjunctivitis (VKC)

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of VKC. The study should compare the test product versus the reference product. Each product is applied four times daily (morning, noon, afternoon, and evening) in each affected eye for four months.

2. Inclusion criteria:
   a. Male or female patients aged 4 to less than 18 years
   b. Females of childbearing potential should be non-pregnant and use highly effective birth control
   c. History of at least 1 recurrence of VKC in the past year prior to the study
   d. Patients not receiving any treatment for VKC
   e. Active severe VKC: grade 3 or 4 of Bonini scale with severe keratitis (grade 4 or 5 on the corneal fluorescein staining (CFS) grading system [e.g., Oxford grading system])
   f. Mean score of 4 subjective symptoms (photophobia, tearing, itching and mucous discharge) ≥ 60 mm using a 100 mm visual analogue scale (VAS)

3. Exclusion criteria:
   a. Any relevant ocular anomaly other than VKC interfering with the ocular surface including trauma, post radiation keratitis, severe blepharitis, rosacea, corneal ulcer, etc.
   b. Abnormal lid anatomy, abnormalities of the nasolacrimal drainage system or blinking function in either eye
   c. Active herpes keratitis or history of ocular herpes
   d. History of ocular varicella-zoster or vaccinia virus infection
   e. Active ocular infection (viral, bacterial, fungal or protozoal infection)
   f. Any ocular diseases other than VKC requiring topical ocular treatment during the study
   g. Wearing contact lenses during the study
   h. Topical and/or systemic use of corticosteroids within 1 week prior to the study
   i. Topical use of cyclosporine, tacrolimus or sirolimus within 90 days prior to the

study
   j. Scraping of the vernal plaque within one month prior to the study
   k. Ocular surgery within 6 months prior to the study (excluding surgical treatment of the vernal plaque)
   l. Acute or chronic diseases that potentially affect efficacy outcome of VKC
   m. Presence or history of severe systemic allergy
   n. Any intake of systemic immunosuppressant drugs within 90 days prior to the study
   o. Known hypersensitivity to one of the components of the study drugs or procedural medications (e.g., fluorescein)
   p. Pregnant or lactating states

4. The protocol should include a list of the prescription and nonprescription/over-the-counter drug products, and activities that are prohibited during the study, such as:
   a. Topical and/or systemic use of corticosteroids
   b. Topical use of cyclosporine, tacrolimus or sirolimus
   c. Antibiotics, pilocarpine, antihistamines or any other topical ocular treatments other than the study medication. Rescue medicine (e.g., dexamethasone) is allowed provided that its use follows the instruction described in the protocol.
   d. Ocular surgery (excluding surgical treatment of the vernal plaque)
   e. Any artificial tears except in case of worsening of the VKC symptoms and inability to have a visit for rescue therapy (unpreserved artificial tears are allowed for patients who are unable to reach the investigator to evaluate the need for rescue therapy)
   f. Contact lenses wear during the study
   g. Systemic immunosuppressive drugs

5. Rescue therapy (e.g., dexamethasone) should be provided for patients who show worsening keratitis and/or worsening symptoms. The conditions for rescue therapy and treatment methods should be described in the protocol.

6. The optimal technique for ophthalmic instillation of the study product should be instructed to subjects and parents or guardians by un-blinded study staff. They should also be informed of the possible side effects (e.g., eye pain and pruritis) following the use of cyclosporine ophthalmic emulsion prior to the application of the study product.

7. The recommended co-primary endpoints are the changes in CFS score (sign) and the ocular itching score using VAS (symptom) from baseline to Month 4 (±3 days). The evaluation methods for the sign and symptom should be clearly defined in the protocol to maintain consistency.

8. 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 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.

9. 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. Site identifier for the study
    d. Study site identifier (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of planned treatment
    j. Name of actual treatment
    k. Safety population flag (yes/no)
    l. Reason for exclusion from safety population
    m. Modified Intent-to-Treat (mITT) population flag (yes/no)
    n. Reason for exclusion from mITT population
    o. Per-Protocol (PP) population flag (yes/no)
    p. Reason for exclusion from PP population
    q. Randomized population flag (yes/no)
    r. Date/time of first exposure to treatment
    s. Date/time of last exposure to treatment
    t. End of study date
    u. End of study status
    v. Duration of treatment (total exposure in days)
    w. Completed the study (yes/no)
    x. Reason for premature discontinuation of subject
    y. Subject required permanent discontinuation of the treatment (yes/no)
    z. Subject required temporary suspension and resumption of the treatment (yes/no)
    aa. Use of rescue medicine or additional treatments (yes/no)
    bb. Baseline CFS score
    cc. Baseline itching score
    dd. CFS score at 4-Month
    ee. Itching score at 4-Month
    ff. Treatment compliance: number of missed doses per subject
    gg. Adverse event reported (yes/no)
    hh. Concomitant medication (yes/no)

10. 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 (if applicable)
    n. Number of days since baseline visit
    o. CFS score
    p. Itching score
    q. Use of rescue medicine since the last visit (yes/no)
    r. Adverse event reported during this visit (yes/no)
    s. Concomitant medication reported during this visit (yes/no)

11. 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.

12. 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

Dissolution test method and sampling times: Not applicable

Additional information:

Device:
The reference listed drug (RLD) product is presented in a single-dose vial with a dropper tip. The vial with dropper tip is the device constituent.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device.

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_214965

[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.