

Draft Guidance on Cyclosporine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Cyclosporine

Form/Route: Emulsion/Ophthalmic

Recommended study: 2 Options: *In Vitro* or *In Vivo* Study

I. In Vitro option:

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which “any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

- i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).
- ii. Acceptable comparative physicochemical characterization of the test and RLD formulations. The comparative study should be performed on at least three lots of both test and reference products.

Parameters to measure: Globule size distribution, viscosity, pH, zeta potential, osmolality, surface tension.

Bioequivalence based on (95% CI): Population bioequivalence based on D_{50} and SPAN ($D_{90}-D_{10}$)/ D_{50} or polydispersity index for the globule size distribution only (the other parameters do not require population bioequivalence analysis). The population bioequivalence analysis should be performed separately for each peak detected in the globule size distribution of the RLD. The separation of the peaks should be determined by the minimum value located between the peaks of the RLD.

- iii. Acceptable comparative in vitro drug release rate tests of cyclosporine from the test and RLD formulations.

An in vivo BE study with clinical endpoint is requested for any generic cyclosporine ophthalmic emulsion, 0.05% that has a different inactive ingredient, a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD, or unacceptable data from in vitro comparative studies.

II. In Vivo option:

Recommended studies: 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint

Design: Randomized, double blind, parallel, placebo-controlled, in vivo

Strength: 0.05%

Subjects: Healthy males and females whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (KCS).

Additional comments: It does not appear that conducting a BE study with clinical endpoint for this drug product would be feasible or reliable due to the modest efficacy demonstrated by the RLD. If a sponsor opts to conduct a BE study with clinical endpoint, it is recommended that the protocol be submitted for review to the OGD Division of Clinical Review.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on: Clinical endpoint (in vivo option)

Dissolution test method and sampling times: Not Applicable