

## Draft Guidance on Cyclosporine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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| <b>Active Ingredient:</b>  | Cyclosporine                           |
| <b>Dosage Form; Route:</b> | Emulsion; ophthalmic                   |
| <b>Strength:</b>           | 0.05%                                  |
| <b>Recommended Study:</b>  | 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:

- i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)<sup>1</sup> and quantitatively (Q2)<sup>2</sup> the same<sup>3</sup>.
- ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The comparative study should be performed on at least three exhibit batches of both test and RLD products<sup>4</sup>.

**Parameters to measure:** Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension. Sponsors should use a dynamic light scattering method (or PCS, QELS) to measure the globule size of the test and RLD formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions. Information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement should be provided.

Sponsors should also submit information on the drug distribution in different phases within the formulation in addition to the six previously identified physicochemical properties (i.e., globule size distribution, viscosity, pH, zeta potential, osmolality, and surface tension).

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<sup>1</sup> Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

<sup>2</sup> Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within  $\pm 5\%$  of those used in the reference product.

<sup>3</sup> No changes (source, grade, etc.) should be made to the structure forming excipient or solubilizing excipient in the product for commercial batches unless adequate supporting data and risk assessment are provided to demonstrate that the changes will not affect the product performance and quality.

<sup>4</sup> All 3 exhibit batches should be at least 1/10 the size of the commercial batch and the manufacturing process used for the 3 exhibit batches should be reflective of the process used for the commercial batch.

**Bioequivalence based on (95% upper confidence bound):** Considering the fact that the shape of the globule size distribution of this product may not be mono-modal, the conventional population BE based on D50 and SPAN may not be sufficient to demonstrate bioequivalence.

Instead, the equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks) should be demonstrated by a method proposed by the sponsor. A statistical metric is preferred to assess the difference (e.g., in terms of distance) between the shapes of distribution profiles. One suggested approach is the earth mover's distance (EMD)<sup>5</sup> method, which computes the minimal cost needed to transform one distribution into the other using an optimization algorithm. An average profile of all RLD samples (i.e., RLD center) is calculated and served as the reference profile to compute the distance between a RLD or a test sample to the RLD center. After obtaining the profile distances between each RLD sample and the RLD average ('RLD' – 'RLD center' distance), and the profile distances between each test sample and the RLD average ('TEST' – 'RLD center' distance), a statistical metric should be employed to quantify the difference between the two categories of distances. One suggested method is the population BE test<sup>6,7</sup>. In order to properly account for variability of the reference product and to achieve adequate power, a sufficient number of samples and replicates should be used.

The other physicochemical parameters do not need population BE analysis.

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

An in vivo BE study with clinical endpoints is requested for any generic cyclosporine ophthalmic emulsion, 0.05% that has a different inactive ingredient from the RLD, 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.

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## II. In vivo option:

**Recommended studies:** One study

Type of study: BE study with clinical endpoint

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

Strength: 0.05%

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<sup>5</sup> Yossi Rubner, Carlo Tomasi and Leonidas J. Guibas. The earth mover's distance as a metric for image retrieval. *International Journal of Computer Vision*, 40(2):99-121, 2000

<sup>6</sup> Guidance for Industry – Statistical Approaches to Establishing Bioequivalence.  
<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf>

<sup>7</sup> Please note that the proposed EMD/PBE method may not be the only approach for globule size profile comparison. Sponsors may also propose their own statistical approach.

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

**Bioequivalence based on:** Clinical endpoint (in vivo option)

**Dissolution test method and sampling times:** Not applicable