Cyclosporine ophthalmic emulsion, 0.05%, is a topical immunomodulator which is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular infection associated with keratoconjunctivitis sicca. Currently, the FDA recommends two options to demonstrate bioequivalence (BE) for cyclosporine ophthalmic emulsion: (1) a clinical endpoint study or (2) in vitro studies with comparative physicochemical characterization. FDA posted a bioequivalence product-specific guidance on cyclosporine ophthalmic emulsion in June 2013, which was revised in February 2016 to include additional guidance on the conduct of the in vitro studies. A summary of scientific considerations when conducting studies to support the in vitro option will be presented.

Methods
For development of the in vitro option, a systematic approach was adopted to identify the physicochemical parameters that are critical for ocular bioavailability and BE of cyclosporine ophthalmic emulsion. In addition, the physicochemical properties of the reference product were determined by several different FDA laboratories to gain understanding of the drug product characteristics.

Results
Formulation excipients influence the critical physicochemical properties of ophthalmic emulsion products; hence, the test formulations should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product. The globule size distribution (GSD) of cyclosporine emulsion can range from a few nanometers up to a micron depending on the instrument and sample preparation method used. Due to the inherent limitation of each GSD measurement technique, one single method may not be adequate to measure the entire size range. Therefore, complementary methods that are capable of measuring globules at the smaller and larger size ranges should be used. In addition, if the GSD is found to be multimodal, a high resolution analysis mode, i.e., narrow mode for laser diffraction (LD) and dynamic light scattering (DLS) methods should be used. GSD should be measured for undiluted samples and upon serial dilution, and the analysis mode, correlation curve (for DLS), dilution condition, dilution medium and histogram raw data should be reported. Since it is relatively difficult to control the extent of dilution for LD, an optimized %obscuration should be kept constant for all measurements to ensure similar concentrations of the test and reference products in the measurement beaker. For LD, the test and reference products can be statistically compared based on Dv,50 and SPAN. For DLS, intensity weighted size distribution, Dv,50 and SPAN, along with harmonic intensity-weighted average particle diameter and polydispersity index can be reported to adequately represent the multimodal size distribution. D50 and SPAN should be evaluated using the population bioequivalence approach. In addition, equivalence between the test and RLD formulations in the shape of the GSD (such as the presence of multiple peaks) should be demonstrated by a suitable statistical method.

Cyclosporine ophthalmic emulsion demonstrates a non-Newtonian shear-thinning property; therefore, a full viscosity profile with varying applied shear rate, instead of a single point viscosity, should be compared between the test and reference products. Cyclosporine is likely to be heterogeneously distributed in different sized globules, e.g., oil globules, micelles. Since a variation in distribution within the formulation may lead to differences in drug release and bioavailability, test and reference products should have a similar drug distribution in each phase of the formulation. A suitable separation method should be developed to quantify the drug distribution without compromising the integrity of the formulation. Along with GSD, viscosity profile and drug distribution, comparison of pH, zeta potential, osmolality and surface tension should also be conducted. Since differences in manufacturing processes have been reported to affect critical physicochemical parameters of cyclosporine ophthalmic emulsion, manufacturing the test batches (at least 1/10th in size of the commercial batch) using the same process as that of the commercial batch should be used in comparative characterization studies.

Comparative in vitro drug release is also recommended because drug release measurements are useful in evaluating the effect of manufacturing differences. Due to the lack of compendial in vitro release methods for ophthalmic emulsion products, a validated method that can discriminate the effect of process variability in the production of the test formulation should be developed. The method validation should include sensitivity, specificity, and selectivity studies.

Conclusion
The revised draft guidance on cyclosporine ophthalmic emulsion provides further essential details on the in vitro BE study parameters and the evaluation criteria. An in vivo BE study with clinical endpoint 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. The revised draft guidance was posted on FDA’s website in February 2016 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358114.pdf.

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