Dry Eye: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Wiley Chambers at 301-796-0690.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors regarding eligibility criteria, trial design considerations, and efficacy endpoints to enhance clinical trial data quality and to foster greater efficiency in development programs for drugs for the treatment of dry eye.[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. CONSIDERATIONS FOR CLINICAL TRIALS

A. Trial Design

Sponsors developing drugs for the treatment of dry eye should consider the following regarding trial design:

- Both traditional environmental exposure trials and challenge-model trials (utilizing a controlled chamber with regulated temperature, air flow, humidity, etc.) can be acceptable.

[1] This guidance has been prepared by the Division of Ophthalmology in the Center for Drug Evaluation and Research at the Food and Drug Administration. For biological products regulated by the Center for Biologics Evaluation and Research, sponsors should contact the Office of Tissues and Advanced Therapies.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

- FDA recommends parallel, randomized by patient, double-masked trials in which the investigational drug group demonstrates superiority over the control group (control agent can be the vehicle).

- Trials in which the investigational drug is used as an *add-on* to a standardized treatment regimen are also acceptable.

- FDA recommends that efficacy be demonstrated in single-day, controlled environment trials or in multiday, natural exposure trials of 2-weeks duration or longer. FDA recommends that safety trials be conducted at least 6 weeks in duration if efficacy trials are of shorter duration.

B. Comparator

Sponsors developing drugs for the treatment of dry eye should consider the following regarding comparative clinical trials:

- Water is known to be an effective component of topically applied treatments for dry eyes. Therefore, in general, comparative clinical trials should use the investigational drug's vehicle as a control agent.

- Trials should demonstrate statistical and clinical superiority over a vehicle control or another treatment regimen.

- Clinical trials for the treatment of dry eyes, even with known effective therapies, can fail to demonstrate efficacy. In the absence of good assay validation (sensitivity) methods (inclusion of both a positive and negative concurrent control), FDA does not recommend equivalence or noninferiority trials.

C. Trial Population

Sponsors developing drugs for the treatment of dry eye should consider the following regarding trial population:

- The sponsor should enroll patients with ocular complaints consistent with dry eye symptoms. Inclusion criteria should include both objective signs and subjective symptoms.

- Patients from relevant demographic subsets should be studied, including both men and women and multiple age, racial/ethnic, and eye color groups.

- Dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatricial pemphigoid) or the destruction of conjunctival goblet cells (as with vitamin A deficiency) represent a specific, severely affected patient population. In general, these are considered separate indications, and patients with these conditions should be studied separately from routine dry eye conditions.

- Severe blepharitis or obvious inflammation of the lid margin can interfere with the interpretation of trial results. In general, patients with these conditions should be studied separately from routine dry eye conditions.

D. Efficacy Considerations

Sponsors developing drugs for the treatment of dry eye should consider the following regarding efficacy:

- In general, safety and efficacy should be demonstrated in at least two adequate and well-controlled, multicenter independent trials.

- FDA recommends that the sponsor demonstrate one of the following:

  – A statistically significant difference between the investigational treatment and vehicle for at least one objective prespecified sign of dry eye (mean group score of test versus vehicle) **and** at least one subjective prespecified symptom of dry eye (mean group score), or

  – A statistically significant difference between the percentage of patients achieving a complete resolution of corneal staining, or

  – A statistically significant difference between the percentage of patients achieving a 10-millimeter increase or more in Schirmer's tear test scores.

- If a sign and a symptom are used to demonstrate efficacy, FDA recommends a number of different endpoints for an objective sign or subjective symptom (see bullet points below).

- Signs of dry eye include, but are not limited to, corneal staining, conjunctival staining, decreased tear breakup time, and decreased Schirmer's tear test score (with or without anesthesia).

- Symptoms of dry eye include, but are not limited to, blurred vision, light sensitivity, sandy or gritty feeling, ocular irritation, ocular pain or discomfort, and ocular itching. Subjects can self identify their own term for ocular discomfort, which can be used in place of any other term.

- A subjective symptom improvement can also be demonstrated by showing a statistically significant difference between the percentage of patients achieving a complete resolution of the symptom. FDA does not recommend the use of anything less than complete resolution (complete clearing of a sign or symptom) for a responder analysis.

- Efficacy for a sign and efficacy for a symptom do not have to be demonstrated in the same clinical trial, but each should be demonstrated in more than one clinical trial.

- The sponsor should discuss with FDA any scoring methods or scales used to measure efficacy variables and should submit a copy of the scoring methods or scales with the protocol.

- FDA recommends that at least one of the clinical trials include treatment of patients with the proposed final market formulation.

E. Safety Considerations

Sponsors developing drugs for the treatment of dry eye should consider the following regarding safety:

- The clinical program should include enough patients to identify adverse drug events that occur at a rate of 1 percent or greater. To accomplish this, FDA recommends that approximately 400 or more patients using the investigational drug complete treatment with a concentration of the investigational drug at least as high as proposed for marketing and with a frequency at least as frequent as proposed for marketing.

- Before submission of a marketing application, the sponsor should ensure that least 300 patients have completed at least 6 weeks of follow-up after the initiation of treatment and at least 100 patients have completed 12 months of follow-up after the initiation of treatment.

- For reformulations of drug substances that are already approved in the same dosage form, same route of administration, and the same or lower concentration, FDA recommends the sponsor ensure that a marketing application has safety information from at least 100 patients treated for at least 6 months.

F. Clinical Evaluations

Sponsors developing drugs for the treatment of dry eye should consider the following regarding clinical evaluations:

- At a minimum, FDA recommends that the following evaluations be performed in each eye and reported separately for each eye (regardless of which eye or eyes are treated):

  – Best corrected, distance visual acuity (4 meters in distance or more) at every visit.

  – A patient comfort examination before and after drug administration at every visit.

  – A slit lamp examination of the anterior segment that includes the cornea, conjunctiva, anterior chamber, iris, lids, and lashes. At a minimum, examinations should be performed at baseline, midway through the trial, the end of treatment, and 2 weeks after treatment discontinuation.

175 – Endothelial cell count, systemic clinical and laboratory evaluations, and dilated fundus
176 examinations at baseline and at the end of trial or at month 3 (whichever is later) in at
177 least one trial.
178
179 **G. Pediatrics**
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181 Dry eye rarely occurs in the pediatric population. Sponsors should consider pediatric assessment
182 waiver requests when submitting their required pediatric study plans under the Pediatric Research
183 Equity Act.[3]
184

[3] See section 505B(e)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(A) of the FD&C Act; 21 U.S.C. 355c(a)(1)(A).