

PANEL QUESTIONS

Endothelial Cell Density

Dr. Michael Grimmert lead responder

Information about the endothelial cell density study is found in the following sections: Study population/ inclusion criteria (Section 5, Table 1 and Attachment B) , examination schedule (Table 2), testing methodologies (Section 8.2), study analyses (Section 9) and sample size (Attachment A.2).

- A. Please comment upon the recommended inclusion criteria recommendations found in Table 1. Note that these recommendations are currently under discussion, so we appreciate any comments you may have.

- B. FDA recommends that “The number of patients should be sufficient to detect a yearly endothelial cell loss of 2.0% and to demonstrate linearity of the cell loss over time.” Our calculations suggest that 200 subjects should be sufficient to detect a 2.0% loss (although it is recommended that specular microscopy be performed on all subjects to ensure that 200 analyzable photographs are obtained), using measurements at multiple visits (at the 3 or 6 month, 12, 24, and 36 month visits) to establish linearity of the loss. FDA has also recommended that multiple images be captured at each visit and the mean endothelial cell density from those multiple images be used in the analysis. Please comment.

- C. Please provide any additional comments on the endothelial cell density study.

Evaluation of the Natural Lens for Cataractogenesis
Dr. William Mathers lead responder

Currently, FDA recommends the following regarding the evaluation of the natural lens for cataractogenesis:

The natural lens should be evaluated preoperatively and at each of the postoperative intervals. The level of evaluation should be commensurate with the risk of cataractogenesis/lens changes identified by the risk analysis performed by the manufacturer. For phakic IOLs where the design or surgical procedure may lead to lens changes, a grading system or quantitative method should be used to evaluate lens changes over time. For IOLs for which lens changes are not an identified risk, qualitative observations may be adequate.

Analyses should include:

- ?? the number of patients with lens changes (i.e., any change in the appearance of the lens, with stratification by the type of change)
- ?? the number of patients with clinically significant lens opacities - *the term "clinically significant" to be defined*
 - A. Please comment on whether you believe evaluation of lens changes should be requested of all sponsors of phakic IOL studies, or whether this evaluation should only be performed if the sponsor's risk analysis warrants evaluation of lens changes.
 - B. Do you have any specific recommendations for defining the term "clinically significant" lens opacities? In the past, a cataract has been considered to be clinically significant if accompanied by a loss of 2 lines or greater BSCVA. Note that FDA, and the Panel, has previously requested that all lens changes being reported by the sponsor. Please consider whether any recommendations can be made with respect to the clinical significance of various degrees of lens opacities.
 - C. Please comment upon the use of quantitative methods for measurement of lens changes versus the use of the more semi-quantitative grading system.
 - D. Phakic IOL studies in the U.S. are currently being conducted with a study duration of 3 years. Based upon the previous discussion of phakic IOL guidance with the Panel, FDA understood the Panel to recommend that 3 years of follow-up data should be collected prior to Panel review. Alternately, the Panel review could be conducted earlier with post-approval studies to collect the remainder of the data. Please comment on the duration of the study and the timing of the Panel's review for this particular endpoint of cataractogenesis.
 - E. Please provide any additional comments on the evaluation of lens opacities.

Contrast Sensitivity Substudy

Dr. Mark Bullimore lead responder

At the most recent American National Standards Institute (ANSI) meetings, which are attended by the ophthalmic industry, ophthalmologists in private practice and in academia, and FDA, consensus appeared to be reached on the general parameters of the contrast sensitivity substudy (as outlined in Section 8.3). In particular, use of contrast sensitivity systems (rather than contrast acuity) was recommended because of its ability to capture the full range of spatial frequencies and contrasts. [It should be noted that best corrected visual acuity testing will also be performed under mesopic conditions to assess letter recognition performance under low light conditions.] Contrast sensitivity testing should be performed under mesopic and mesopic with glare conditions. These conditions were chosen to test subjects under worse case conditions, and to minimize the amount of testing required.

- A. Please comment on the clinically significant decrease in contrast sensitivity being set at 0.3 log units (see B.3). For clinical significance, should this drop be at 2 or more spatial frequencies or is one spatial frequency sufficient?
- B. Should charts with a minimum amount of grating contrast at each spatial frequency be recommended, e.g. each row of gratings should include grating contrasts up to 40% or 60% (to minimize the missing data problem – see below)? If so, are these charts commercially available?
- C. Please comment upon recommended analyses of these data, including the handling of missed data (i.e., subject unable to see targeted spatial frequency at any contrast).
- D. Please provide any additional comments on the contrast sensitivity substudy, including any other guidance that could be provided to enhance the quality of the data that are generated from this testing.