

MEMORANDUM

Date: April 20, 2000

To: Members of the Ophthalmic Devices Panel

From: Sara M. Thornton, Executive Secretary
Ashley A. Boulware, Biomedical Engineer

Re: Questions for consideration regarding clinical studies of refractive implants

Members of the Panel:

Thank you for agreeing to evaluate FDA's proposals for clinical studies of refractive implants. You have been sent the entire section on clinical studies that will be incorporated into a guidance document. However, there are several questions we would like you to address initially. These are the questions we plan to discuss on May 12. If time allows, we will discuss any other comments you might have regarding the proposals. Additionally, the draft guidance document, when it issues, will be open for comment for a period of at least 90 days, and any additional comments you might have may be submitted to FDA.

Scope of the document

1. The current scope of the document includes ocular implants intended for implantation in a phakic eye as well as IOLs intended for clear lens exchange.
 - a. Do you agree that IOLs intended for clear lens exchange should be included in the scope of this document?
 - b. If yes, are there additional clinical evaluations and/or safety and efficacy endpoints that should be added for this indication?
 - c. If yes, are there additional or different inclusion and exclusion criteria that should be applied for studies of these devices? E.g., should a maximum axial length criterion be added?

Endothelial cell counts

2. FDA is proposing a substudy of 200 subjects with endothelial cell counts measured preoperatively and at 3 (or 6) months, 1 year, 2 years and 3 years. This substudy should demonstrate the rate of surgical loss (preoperative to 3 or 6 months) and the rate of chronic loss of endothelial cells.
 - a. FDA has suggested a maximum rate of surgical loss of 10%. Do you agree that this rate is reasonable?
 - b. Assuming a standard deviation of 5%, the sample size of 200 subjects should allow the detection of a rate of chronic loss greater than 1.5% per year. We have estimated that a patient who receives an implant at age 21, has a 10% loss due to surgery, and

has a 1.5% per year chronic loss will still have 1000 cells until approximately age 88. Is the rate of 1.5% per year a reasonable target value for chronic cell loss?

- c. We have included recommendations regarding the analysis of endothelial cell counts. For example, for corneal and anterior chamber refractive implants, both central and peripheral counts should be taken. What is your recommendation for the location of peripheral counts (i.e., 3 mm from the center, etc.)? Do you have additional recommendations?
- d. We have recommended that analyses include:
- the mean rate of cell loss over time, calculated via a paired analysis in order to calculate the mean of the differences
 - a frequency analysis examining the percentage of patient who lose greater than 10% of cells between Month 3 (or Month 6) and Month 36.

Do you agree with these recommendations? Are there additional analyses that should be performed?

Cataractogenesis

3. FDA has recommended that the crystalline lens be evaluated preoperatively and at each of the postoperative visits using a standardized grading system and photographs.

- a. Do you agree that the LOCS III and Oxford grading systems are adequate for this evaluation? Would you recommend other grading systems? Do you have additional recommendations about this evaluation?
- b. We have recommended that analyses include:
- the percentage of subjects with lens changes (i.e., any change in the appearance of the lens, with stratification by the type of change)
 - the percentage of subjects with clinically significant lens opacities (defined as opacities leading to a loss of 2 or more lines of BSVCA with glare as compared to preoperative levels adjusted for magnification/minification effects)

Do you agree with these recommendations? Are there additional analyses that should be performed?

- c. We have also recommended that the inclusion criteria include age limits in an attempt to avoid age-related cataract formation as a confounding variable. However, the age limit for hyperopic subjects (60 years of age) has been established as somewhat higher than that for myopes (50 years of age), given the mean age of the population and the smaller numbers of potential subjects.
- i. Do you agree that age limits should be established to avoid age-related cataract as a confounding variable?

- ii. If yes, do you agree with the proposed limits?
- iii. If no, should all cataract formation be ascribed to the device or should some other analysis be performed to demonstrate the rate of cataract directly related to the device?