

## Posterior Capsular Opacity Evaluation in IOL Clinical Studies Discussion Paper

### INTRODUCTION

The comparison of posterior capsule opacification (PCO) incidence data between IOLs has been difficult due in part to the lack of standardized methodology for objective evaluation of the posterior capsule. In addition, the presence of a certain degree (density or area of extent) of PCO is not invariably correlated with a similar impact on the subject's visual function. Attempts to use Nd:YAG capsulotomy rate as a surrogate for PCO rate have been confounded by subjective variability in the clinical criteria used and the timing of intervention.

FDA has prepared this document to aid sponsors in the development of clinical studies that support PCO claims in IOL labeling.

Early discussion with FDA regarding specific PCO study proposals and desired labeling claims is highly recommended.

### GENERAL STUDY GUIDELINES

The following suggestions should be considered in the design of PCO studies.

The study should employ an accepted methodology for the measurement and grading of PCO, as recommended by the FDA advisory panel on 5/11/00. [*list acceptable methods or elements of methods with references*]. FDA will also consider other valid objective methods of PCO evaluation with acceptable documentation. Issues such as reliability and reproducibility of the method, criteria for differentiating imaging artifacts, and evaluation of an acceptable region of interest (central 3mm at a minimum) should be addressed.

The target outcome is incidence of "clinically significant PCO," defined as objectively documented PCO associated with a minimum decline of >2 lines in the subject's visual function, either BCVA or glare acuity [*visual function measures and minimum degree of impact per panel discussion*].

Alternatively, sponsor may choose to use Nd:YAG capsulotomy rate as a surrogate outcome for PCO incidence. In this case, the study protocol must standardize the minimum threshold clinical conditions for performance of a capsulotomy. The capsulotomy must be "clinically justified" by demonstration of a >2 line improvement in the subject's visual function post-capsulotomy, either BCVA or glare acuity.

The trial design should attempt to achieve masking of the post-op evaluator for the IOL. Randomization should be used to assign subjects to control and trial IOLs. In choosing a control IOL, consideration should be given to such factors as lens material and design. The choice of control lens may affect the type of claim approvable for labeling and also for new technology IOL designation by HCFA, thus early discussion with FDA is recommended.

The protocol should be standardized for the following aspects of surgical technique, all of which theoretically affect PCO development: incision size, capsulorhexis size, use of capsule polishing, intra-op and post-op medications.

Control and trial IOL populations should be matched for age.

FDA suggests that sample size be based on a statistical analysis that incorporates the following factors: desired level of delta (minimum delta suggested by FDA advisory panel) and anticipated trial and control IOL PCO rates.

Consideration should be given to the potential influence of systemic and ocular factors on subsequent development of PCO. Possible confounding effects should be minimized by exclusion of certain subjects from study. Current literature suggests exclusion of subjects with the following conditions: pseudoexfoliation syndrome, uveitis, non-age-related cataracts, previous intraocular surgery or laser treatment, diabetes, glaucoma, current use of systemic steroids or topical ocular medications, previous use of cytotoxic drugs or total body irradiation, and previous ocular trauma.

Intraoperative exclusions should occur for tear in the capsulorhexis, zonular dehiscence, posterior capsule rupture, vitreous loss, and other unexpected surgical complications which could reasonably be assumed to affect PCO development.

PCO evaluations should be consistent with the time frames suggested for typical IOL clinical studies (FDA's IOL guidance document suggests day 1, week 1, month 1, month 4-6, and years 1, 2, and 3). In addition to these scheduled visits, sponsor should consider additional evaluations.

Data analysis should be stratified by investigator and by cataract grade.

The consent document should inform the subjects that due to the investigational nature of the study, Nd:YAG capsulotomy will not be performed, despite subjective symptoms, unless visual function decline meets the objective requirements stated in the clinical protocol.