

FDA Panel Meeting May 12, 2000

Posterior Capsular Opacity Rate Superiority Claims For IOL Studies

In the review of the issue of posterior capsular opacification, we are being asked to develop a means of determining superiority or advantages of intraocular lenses compared to existing intraocular lenses pursuant to the new technology intraocular lens regulations from HCFA. This is something different than what we have done in the past in that we are being asked to structure a means to determine whether a device is better than a prior device. This is unlike the 510K process which looks for "substantial equivalence" or our usual reviews which seek to determine safety and efficacy and in the past have precluded direct comparisons with specific products.

In response to the questions on clinical endpoints:

- 1) Since not all measurable PCOs are associated with clinically significant effects on a subject's visual function, do you believe that demonstration of decline in measures of visual function should be a required endpoint for a PCO Study? If so, what degree of visual impact do you recommend? If not, what quantitative measurement of PCO grade do you recommend as an appropriate endpoint?

It is my feeling that either a demonstrated decline in visual function or a significant quantitatively measured occurrence of posterior capsular opacification should be an appropriate endpoint. For visual function, this would be a decline in acuity of 2 lines or more under standard (ETDRS) testing or a decline in 2 lines or

more with brightness acuity testing. Similar decreases in contrast sensitivity would also be acceptable. Straylightmeter testing could also be used to demonstrate opacification, although I do not have sufficient familiarity with this technique to know what level would be an appropriate endpoint. For quantitative measurement of PCO grade Scheimflug or high resolution retro-illumination photography with digital analysis would be appropriate techniques, but the exact level to use as an endpoint, again, because of my lack of experience with these techniques, is uncertain.

- 2) Is a claim of delay in onset of visually significant PCO within the study clinically relevant? If so, what period of time do you consider a clinically significant delay?

If posterior capsular opacification is to occur and be clinically significant, it probably doesn't matter whether it occurs in the first few months or the first couple of years after surgery, since in either case it would need to be treated. While delay in onset, if demonstrated in a given study, would be of interest, the significance is uncertain. The only clinically significant delay would be one that was greater than several years.

- 3) What minimal difference in PCO rate between two IOLs do you consider clinically significant, for which a claims superiority should be considered? Do you suggest a minimal number of subjects allowable for such a study?

It is difficult to answer this question. Any significant reduction in posterior capsular opacification has both clinical and economic relevance. A claim of superiority based on a 10% difference, assuming accurate and reproducible measurements, should be considered. Given the sample-size analysis table provided, a sample size of 150 per group would be reasonable.

Study controls:

- 1) What factors should be considered in choosing an appropriate control IOL? Is there is a "gold standard" control lens or PCO rate that could be designated by FDA in order to permit intra-study comparisons of PCO incidence?

While the "gold standard" in the past has been the PMMA lens, more recently silicone and acrylic lenses have been demonstrated to have lower PCO rates. It would be unfair to ask that NT IOLs demonstrate substantial benefit over acrylic lenses, which have, at present, the lowest PCO rate. Probably standard PMMA lenses should remain, for the present, as the gold standard.

- 2) What factors are important to be matched in the trial and controlled populations?

Surgical techniques, exclusion criteria (see below) and patient ages should be matched in the trial and control groups.

- 3) With regards to the HCFA NT IOL designation, what additional considerations must be factored into the choice of a control IOL for the sponsor to demonstrate superiority over all IOLs? Do you believe it is feasible to allow of superiority over all IOLs with respect to PCO rate?

In addition to the optic material, haptic material needs to be taken into consideration for a control IOL as does optic and haptic design. This includes factors like "laser ridges", edge design, and optic design (posterior surface convex, plano, etc.). While it is feasible to allow claims of superiority over all IOLs, it is more realistic to expect relative superiority over whatever gold standard is chosen.

Methodology:

- 1) Regarding current methods of PCO analysis, do you consider particular methods acceptable for PCO IOL studies? Are there particular criteria that you consider critical? Do you consider any of the current methods not valid?

Do you think that subjective clinical grading systems should be permitted? The current methods in the literature provided to us for analyzing PCO are quite acceptable. While particular criteria including area of capsule evaluated, reproducibility of measurements, and method of assessment are important, subjective clinical grading systems should be acceptable as well. I do not consider any of the current methods invalid.

Clinical protocol:

- 1) Do you suggest any deletions or additions to the exclusion criteria list?

I would suggest the addition of retinitis pigmentosa as an exclusion criterion because of the higher incidence of capsular opacification and capsule contraction in this disorder.

- 2) What time points do you suggest for PCO assessment? Do you suggest follow-up beyond one year? If so, at what intervals and for what duration?

I feel it would be appropriate to assess PCO at 6, 12, 24 and 36 months.

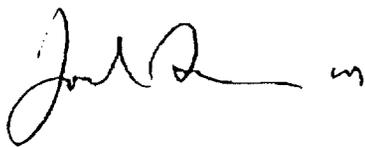
3) What factors are critical to be standardized within a PCO study?

The surgical technique should be standardized with regard to capsulorhexis approximate size, capsule polishing, post-op medications, and measurement techniques. Surgical incision location probably is irrelevant as is surgical incision size. Nuclear removal techniques should be standardized with respect to either all being extracapsular or all being phacoemulsification although the exact technique for phacoemulsification would not need to be standardized between surgeons.

4) See clinical endpoints 1. Do you feel that all PCO studies should evaluate both outcomes (capsulotomy rate and PCO incidence?)

Yes.

Summary question: My recommendations and suggestions are included in the above responses.



Joel Sugar, MD

4/12/00