

SUMMARY MINUTES

OF THE

OPHTHALMIC DEVICES PANEL MEETING

November 30, 2001

OPEN SESSION

**Holiday Inn Gaithersburg
Walker/Whetstone Rooms
2 Montgomery Avenue
Gaithersburg, MD**

OPHTHALMIC DEVICES PANEL MEETING

November 30, 2001

PANEL PARTICIPANTS

Joel Sugar, M.D.	Consultant, Interim Chair, deputized to vote
Arthur Bradley, Ph.D.	Voting Member*
Michael R. Grimmatt, M.D.	Voting Member*
Alice Y. Matoba, M.D.	Voting Member
Jayne S. Weiss, M.D.	Voting Member*
Janice M. Jurkus, O.D.	Consultant, deputized to vote
Jose S. Pulido, M.D.	Consultant, deputized to vote
Timothy T. McMahon, O.D.	Consultant, deputized to vote
Andrew J. Huang, M.D.	Consultant, deputized to vote
Allen C. Ho, M.D.	Consultant, deputized to vote
William D. Mathers, M.D.	Consultant, deputized to vote
Ronald E. McCarley	Industry Representative

*Primary Reviewer for PMA P010018

FOOD AND DRUG ADMINISTRATION PARTICIPANTS

Sara M. Thornton	Panel Executive Secretary
Bernard E. Statland, M.D., Ph.D.	Director, Office of Device Evaluation
A. Ralph Rosenthal, M.D.	Director, Division of Ophthalmic Devices And Ear, Nose and Throat Devices
Everette T. Beers, Ph.D.	Chief, Diagnostic and Surgical Devices Branch

James F. Saviola, O.D.	Chief, Vitreoretinal and Extraocular Devices Branch Acting Chief, Ear, Nose and Throat Devices Branch
Sheryl L. Berman, M.D.	Medical Officer, Division of Ophthalmic and Ear, Nose, and Throat Devices Team Leader, PMA P010018
Joel P. Glover, M.S.	Biomedical Engineer, Intraocular and Corneal Implants Branch Team Leader, PMA P010018

SPONSOR REPRESENTATIVES

Dr. Judy Gordon
Regulatory Consultant to Refractec

Dr. Jon Hayashida
Refractec Vice President for Clinical Affairs

Marguerite McDonald, M.D.
Medical Monitor, Principal Investigator

Peter Hersh, M.D.
Principal Investigator

OPEN SESSION—November 30, 2001**Call to Order and Introductory Remarks**

Joel Sugar, M.D., Interim Panel Chair, called the meeting to order at 9:45 a.m. **Sara M. Thornton, Panel Executive Secretary**, welcomed those present to the 102nd meeting of the Ophthalmic Devices Panel. She stated that the next panel session was scheduled for January 17-18, 2002. Ms. Thornton introduced three new panel consultants: Allen C. Ho, M.D., Andrew J. Huang, M.D, and William D. Mathers, and new Industry Representative Ronald E. McCarley. Ms. Thornton asked the other panel members to introduce themselves and noted with regret that new Consumer Representative Glenda V. Such, M.Ed., was unable to be present for health reasons.

Ms. Thornton read the conflict of interest statement, noting that Michael R. Grimmatt, M.D., had been granted a waiver for his interest in a firm potentially affected by the day's deliberations. Matters concerning Arthur Bradley, Ph.D., Timothy T. McMahon, O.D., and Allen C. Ho, M.D., had been considered but deemed unrelated and their full participation allowed. She also read appointments to temporary voting status for Janice M. Jurkus, O.D., Allen C. Ho, M.D., Andrew J. Huang, M.D., William D. Mathers, M.D., Jose S. Pulido, M.D., and Joel Sugar, M.D. and an appointment as interim chair for Dr. Sugar.

OPEN PUBLIC HEARING

There were no requests from the audience to address the panel. Ms. Thornton read a letter from **I. Howard Fine, M.D.**, President of the American Society of Cataract and Refractive Surgery

and Clinical Associate Professor of Ophthalmology of the Casey Eye Institute, and an unpaid member of the Refractec Medical Advisory Board with no equity in the company. He asked that the panel approve the conductive keratoplasty procedure under consideration on the grounds that it showed clinical trial outcomes as safe and effective as those presented by other refractive technologies and produced little or no postoperative dry eye effect.

OPEN COMMITTEE DISCUSSION

FDA Presentation

Bernard Statland, Director of the Office of Device Evaluation, thanked the panel for its hard work and presented letters and plaques of appreciation to outgoing members Joel Sugar, Janice Jurkus, and Jose Pulido. A similar plaque and letter were being sent to former Industry Representative Marcia Yaross, who had finished her term.

Jose Pulido acknowledged the high quality of those in the FDA who walk a fine line between the needs of private enterprise and the need for public safety. He thanked the FDA for its work in defending the public safety and stated that it had been an honor and privilege to work with members of the Agency.

Division and Branch Updates

A. Ralph Rosenthal, M.D., Director of the Division of Ophthalmic Devices, told the panel that **Eric Mann**, formerly of the National Institutes of Health, had joined the division as the new chief of the Ear, Nose, and Throat Branch.

Everette T. Beers, Ph.D., Chief of the Diagnostic and Surgical Devices Branch, gave the branch update, stating that the branch had been busy reviewing clinical trials and had approved two PMAs—PMA P930016/S14 for VISX for LASIK for mixed astigmatism of less than or equal to 6.00 D in the spectacle plane and P980008/S5 for LaserSight for LASIK for myopic astigmatism of -0.50 to less than -6.00 D SE and up to less than or equal to 4.50 D cylinder.

James F. Saviola, O.D., Chief of the Vitreoretinal and Extraocular Devices Branch, gave the branch update. He described two Ciba Focus NIGHT & DAY soft contact lenses for correction of myopia and hyperopia prescribed for daily or extended wear for up to 30 nights of continuous wear that were reviewed at the July panel meeting and approved on October 11, 2001 and gave their indications, precautions, and selected study results. Dr. Saviola also described a supplement to PMA P980006 for the Bausch & Lomb (B&L) PureVision lenses approved on November 20, 2001 for daily or extended wear from 1 to 30 days between removals for myopia and hyperopia at specified ranges and gave its precautions and restrictions. He noted that the supplement had been scheduled for the September 21 meeting for the panel to discuss the need for a postmarket study and to review clinical data from a contralateral eye clinical study. After cancellation of the September 21 panel meeting, it was decided that the primary clinical issues in the PMA substantially duplicated information previously reviewed by the panel. In lieu of a full panel discussion, homework assignments from two additional panel members were obtained. These corroborated the recommendations of the two primary

reviewers; all panel reviewers recommended that the supplement be approved subject to a postapproval study to assess the long-term rates of microbial keratitis and associated loss of vision.

Dr. Saviola described the approval restrictions on these two extended wear lenses in the areas of advertising (including package inserts and consumer information leaflets), labeling, and postapproval clinical studies. Both the Ciba and the B & L studies will involve about 100 sentinel monitoring sites designed to provide data of 4,500-5,000 patient years of subjects wearing their one-month lenses during a one-year period to give an early indication for risks in the real world setting.

PMA P010018—Refractec's ViewPoint Conductive Keratoplasty (CK) System

Sponsor Presentation

Judy Gordon, DVM, regulatory consultant for Refractec, introduced the sponsor team.

Jon Hayashida, O.D. and vice president for clinical affairs of Refractec, described methods for surgical correction of hyperopia and collagen shrinkage via thermal keratoplasty through laser energy or application of radio frequency energy. After a brief description of the ViewPoint device, Dr. Hayashida provided an overview of the technology involved in conductive keratoplasty (CK). He concluded that CK provides a uniform footprint that leads to the success of the treatment and that use of radio frequency in CK has clinical advantages based on its mechanism of action.

Marguerite McDonald, M.D., medical monitor and clinical investigator, presented clinical results. She outlined the protocol and clinical investigators for the prospective, multicenter clinical trial. Study design was consistent with FDA guidance for refractive surgery laser and draft ANSI

guidance for laser systems for corneal reshaping and aimed for full correction of spherical hyperopia. Dr. McDonald described eligibility criteria, noting that all treatments were based on preoperative cycloplegic refraction spherical equivalent (CRSE). Effectiveness parameters were improvement in uncorrected visual acuity (UCVA), predictability, stability, and patient satisfaction. Safety parameters were preservation of best spectacle corrected visual acuity (BSCVA), induced cylinder, endothelial cell loss, patient symptoms and complications and adverse events. Demographics, baseline refractive characteristics, and preoperative refractive parameters by diopter of all eyes enrolled were all consistent with other refractive trials. Dr. McDonald stated that the nomogram was adjusted after an analysis of the first 54 eyes, and that accountability of all eyes enrolled up to 12 months was excellent. Safety and stability were based on all eyes treated (400), effectiveness on eyes treated with the current nomogram (363).

Dr. McDonald presented effectiveness results, stating that the key effectiveness targets were met according to targets set by FDA. These included improvement in UCVA to 20/40 or better in more than or equal to 85% of eyes with preoperative BSCVA of 20/20 or predictability of MRSE within less than or equal to 0.50 D for 50% of eyes and within less than or equal to 1.00D for 75% of eyes. Post operative stability was defined by the change in MRSE over a 3 month interval of less than or equal to 1.00D for 95%, and mean rate of change in MRSE of less than or equal to 0.5D/year with an asymptote of zero, and a 95% confidence interval for mean change in periods preceding and after stability is established to include zero. A paired analysis of the eyes treated with the current nomogram

to see the percent of intended correction remaining found 94% of intended correction in MRSE remained at 12 months, with 90% of intended correction in CRSE remaining at 12 months. Proportion of intended correction retained beyond 12 months was undetermined. Patient satisfaction showed 31% and 46% of patients to be satisfied or very satisfied at 12 months, which Dr. McDonald said was consistent with other studies of hyperopia.

Dr. McDonald presented a summary of safety of all eyes treated at six, nine, and 12 months according to FDA limits. Criteria for preservation of BSCVA were loss of greater than two lines of BSCVA of less than 5% (CK showed none at 12 months), loss of two lines of BSCVA (CK showed less than 1% at 12 months), BSCVA of worse than 20/40 of less than 1% (CK showed 0), BSCVA worse than 20/25 if 20/20 or better preoperatively (CK showed 0), and increase of more than 2.00 D cylinder of less than 5% (CK showed less than 1%).

Peter Hersh, M.D., clinical investigator, discussed safety limits for induced cylinder, which were induced cylinder of more than 2.00 D in less than 5% of eyes, induced cylinder of greater than 1.00 D reported in labeling for all comparable products for hyperopia treatment, and induced cylinder of more than or equal to 1.00 D reported at FDA's request. He summarized that the CK results were below the FDA safety limit of more than 2.00 D and that the frequency and magnitude of induced cylinder diminish over time. When induced cylinder is present, he said, there is on average one line less improvement in UCVA; UCVA improves over time as induced cylinder resolves. There is no significant effect on BSCVA.

Dr. McDonald discussed the safety parameter of endothelial cell loss, which was targeted to be no more than 10% loss in cell density. Results on all eyes in the substudy showed a less than one percent loss in endothelial cell density over the course of follow-up in any region and no polymegathism or polymorphism. She concluded that radio frequency energy can be safely delivered to the cornea with no effect on the endothelium.

A subjective questionnaire was administered at baseline, one, three, six, nine, and 12 months to rate symptoms as moderate, marked, or severe. Patient symptoms with a more than 5% increase from baseline to month six, nine, or 12, were dryness, glare, halos, double vision, fluctuation of vision, and variations in vision with change in lighting, with the majority reported in the moderate category.

Safety parameters for complications and adverse events included adverse events to occur in no more than 5% of eyes and any single adverse event to occur in less than 1% of eyes. Complications for CK included recurrent corneal erosions, later resolved, a foreign body sensation, later resolved, pain in both eyes, later resolved, and double or ghost images. Device/procedure-related adverse events included a corneal perforation, no RF energy delivered during two treatments, which was corrected and reviewed by FDA, and various clinical events including transient intraocular pressure or mild iritis that resolved without sequelae.

Dr. McDonald summarized the effectiveness results as showing UCVA exceeding FDA targets, accuracy of achieved versus intended correction exceeding FDA targets, 94% of intended correction remaining at 12 months, and no retreatments performed during the study. Safety results showed that all

performance limits identified in the study protocol and FDA guidelines were met, that preservation of BSCVA was established, that the incidence of induced cylinder met the FDA limit, that the induced cylinder decreased in frequency and magnitude over time, with no effect on BSCVA and minimal effect on UCVA, and that there was a very low cumulative incidence of adverse events.

Panel Questions for the Sponsor

Panel questions to the sponsors included the possible need for a contraindication against device use with patients having implanted electrical devices such as defibrillators and cochlear implants, concern over the patient satisfaction levels, the issue of long-term stability and permanence of the procedure, and the possible need for remedial spectacles as results are stabilizing in the postoperative period.

FDA Presentation

Joel Glover, leader for the FDA review team, thanked the sponsors, the panel, and the FDA review team for their help in bringing the PMA to panel.

Sheryl Berman, M.D, Medical Officer, thanked the sponsors for their work. She listed six FDA questions, with accompanying summary tables of data, on incidence of induced cylinder, adequacy of 12-month follow-up, whether the refractive correction justifies the procedural risks, the increased incidence of visual symptoms from preoperative levels, whether the data support approval for the requested indication, and possible labeling recommendations for panel review.

Panel Questions for the FDA

The panel had no questions for the FDA.

Additional Comments from the Sponsors

Sponsor representatives replied to the questions raised by the FDA. Dr. Hersh stated that the rate of induced cylinder is within the current FDA recommended guidance, diminishes over time, and has no significant effect on BSCVA. On adequacy of available follow-up data, Dr. McDonald stated that the available data provide reasonable assurance of safety and efficacy and that sponsors are willing to update the data as further results are available. Similarly, the sponsors thought the potential risks were justified by the significant improvement in UCVA with no serious adverse effects and no removal of tissue. While sponsors thought the FDA's concerns were valid, they noted that such concerns were true of all refractive procedures and that CK offered a viable alternative with a comparable risk/benefit ratio. They discussed various possible labeling changes as well.

Committee Deliberations***Primary Panel Reviews***

Arthur Bradley, Ph.D., raised six issues in his review. He stated that the data should have been presented in graph format and that the original data should have been presented, rather than an analysis of how the data met FDA criteria. Dr. Bradley also expressed concern that the procedure appears to introduce huge variability in refractive error. Similarly, he was concerned that extrapolation of the stability data over a longer period would show the refractive error returning to pre-procedural

levels. He recommended a vector analysis be used in the future to assess whether the procedure induced a random astigmatism or one correlated more directly to treatment spots, and he also suggested a scattergram be used to show interactions with other conditions. Finally, Dr. Bradley urged that the patient consent document must present all issues understandably, in particular the true nature of the procedure, i.e., they weren't going to have a laser irradiating their eye but that a sharp needle is going to be inserted into their eye up to 32 times, and the likelihood, magnitude, and consequences of post-CK myopia and astigmatism for such daily activities as driving.

Michael R. Grimmert, M.D., noted that of the study population of 401, very few had reached the 24-month mark, making the data incomplete. On safety, he expressed concern at the rate of BSCVA loss of greater than or equal to two lines, noting that a 5% rate is not insignificant, even if it decreases with time. He stated that the increase in subjective symptoms such as glare, halos, double vision, fluctuation of vision, variation of vision, and night driving problems suggests higher order visual aberrations are induced. Also, the increase in variation of vision and fluctuation of vision suggests refractive instability. He was concerned about the increase in cylinder magnitude and recommended that appropriate labeling should include specific data regarding cylinder induction rates greater than or equal to 1.00, greater than or equal to 1.50 and greater than or equal to 2.00 diopters. Regarding the etiology of the induced cylinder, he speculated that the high rate of induced cylinder may be due to a combination of factors, e.g., inaccurate spot placement, asymmetric energy uptake, non-perpendicular needle track, and non-uniform needle depth. In light of his concerns about efficacy and refractive

instability based on increased variation and fluctuation of vision, progressive declines in astigmatism magnitude, progressive declines in overcorrections, progressive increases in mean MRSE, and a continuous month-to-month refractive shift, Dr. Grimmatt emphasized that the seemingly transitory nature of this procedure should be communicated to prospective patients, especially as there are no data on retreatment outcomes. He listed seven material facts to be included in the informed consent, saying that he was hard pressed to see that the prudent patient would want this procedure but noting that the FDA's position on temporary devices is that marginally effective devices can be approved for temporary reduction of hyperopia and that such devices have received approval. Dr. Grimmatt thought it mandatory to emphasize the refractive instability as shown by a progressive hyperopic shift and to note that the duration of refractive drift is unknown, with the data insufficient to prove whether the duration is stable or temporary. Dr. Grimmatt listed six recommendations for conditions of approval, with detailed labeling changes.

Jayne S. Weiss, M.D., stated her concern that the induction of axis shift and astigmatism must be addressed in patient and physician labeling because of the potential for causing subjective patient complaints. She stated that the sponsor had provided reasonable assurance of safety and efficacy at the 12-month point, but the panel should discuss use of the word "temporary" in the indication for use to best describe efficacy of CK and address concerns about regression. Dr. Weiss thought the refractive correction obtained with the device did justify the potential risks, although the labeling should be revised to discuss possible complications and increased incidence of visual symptoms from the preoperative

levels. She recommended that the device should be approved with conditions that the data be brought out to 24 months and the labeling amended according to several specific recommendations.

Dr. Rosenthal of the FDA reminded the panel that each PMA must stand on its own merits and that while references could be made to other PMAs, no comparisons could be made.

Panel Discussion of PMA P010018

FDA Questions to the Panel

- 1) *What are the concerns regarding the incidence of induced cylinder with significant axis shift and its consequent effect on efficacy?*

The panel expressed concern over not knowing the cause of induced cylinder while acknowledging that unanswered questions do not preclude approval of the procedure. The panel also expressed concern over the UCVA loss associated with the procedure's variability, inaccuracy, and shifts in cylinder axis. They advised that the labeling should state clearly, in ways the patient can understand, that the study only included patients with low initial levels of astigmatism and that labeling should stratify the rate of induced cylinder by degrees of induction and other variables.

- 2) *Is a 12-month follow-up sufficient to provide reasonable assurance of safety and efficacy? There are 21 eyes available at 24 months. Should data for these eyes also be required in the labeling?*

The panel disagreed on this point, with some wanting the 24-month data to be included for efficacy and others urging that approval be held until more complete data are available to show stability. The majority

of members argued that the device could be approved based on 12-month data if the effects are stated as temporary and that it was impossible to predict what the 24-month data will ultimately show on stability.

3) Does the refractive correction obtained with this device, in light of the rate of change of mean MRSE over time and the incidence of over- and undercorrection, justify the potential risks?

The majority of the panel thought the refractive correction obtained with this device justified the potential risks since the safety risks were minimal, despite the question of stability, although at least one member argued that it was hard to assess if the benefit justified the risk, given that the procedure itself actually increases variability and produces clinically significant levels of myopia for significant numbers of patients.

4) Are there concerns regarding the increased incidence of visual symptoms from pre-op levels?

Again, some members of the panel thought that such visual symptoms were a ubiquitous result with procedures of this sort and had been assessed in an uncontrolled setting. Others expressed concern that patients did not have these symptoms preoperatively but did have problems postoperatively. It was recommended that a table be delineated in the labeling listing symptoms pre and postoperatively.

- 5) *Do the safety and efficacy data presented in this PMA support approval of this device for the requested indication? Is the requested indication appropriate as worded, based on the study outcome?*

The panel had an extensive discussion about the best way to indicate that the procedure appears to produce a temporary and perhaps unstable or changeable result over time. They recommended revising the requested indication for use to read “CK treatment for temporary reduction of spherical hyperopia in the range of...” in the first bullet and revising the fourth bullet to state, “The magnitude of correction diminishes over time.”

- 6) *What are your recommendations for labeling regarding regression of effect, induction of cylinder, and incidence of visual symptoms? Are there additional labeling recommendations?*

The list of labeling issues contained in Dr. Grimmett’s review was read here. He revised his 10th suggestion to ask for data on spectacle or contact lens dependence following the procedure. He deleted his 13th recommendation in light of the newly revised indication. In addition, panel members recommended that any implanted electrical device should be a contraindication. The labeling should make patients aware that overcorrection could be expected and that the recovery time to regular vision will be lengthy. Expectations on immediate postoperative pain should be clarified, as should the description of the actual procedure given in the patient information.

Open Public Hearing

There were no requests to address the panel.

FDA Closing Comments

Dr. Rosenthal thanked the panel, and especially the primary reviewers, for the discussion.

Sponsor Closing Comments

Dr. Judy Gordon thanked the panel and stated that the sponsor would endeavor to convey the panel's suggestions in the labeling and patient information brochures.

Panel Vote

Executive Secretary Sara Thornton read the voting instructions and options. A motion was made and seconded to recommend the PMA as approvable subject to the following conditions:

- 1) The indications are amended, with the first bullet reworded to state "CK treatment for the temporary reduction of spherical hyperopia in the range of..." The last two bullets (regarding diminution of magnitude of correction over time and proportion of intended correction retained) were eliminated. This condition carried by a vote of seven to three.
- 2) Additions to the labeling should be made as listed by Dr. Grimmert, with the modification of BSCVA greater than two lines, corrections to number 10, and the elimination of number 13. In addition, implanted electric devices should be added as a contraindication, and it should be noted that the effect in patients with narrow angles is unknown. In the patient information, the procedure should be better described, including needle placement and deletion of the reference

to gentle heating; it should be added that data beyond 12 months are unavailable, and it should be stated that there is initial overcorrection and it may take six to nine months to reach the full results. This condition was carried by a vote of nine, with one abstention.

3) The study should be completed to the 24-month interval with data submitted to the FDA for review. This condition was carried by a vote of nine, with one abstention.

The vote to recommend the PMA as approvable subject to the above conditions was carried by a vote of nine to one. Those who voted for approval stated that they did so because the device can temporarily and unpredictably but clearly diminish hyperopia. The one member who opposed the motion stated that he thought the device was unreliable, inaccurate, and unstable.

Panel Chair Dr. Sugar stated that he had enjoyed his time as a panel voting member working with the Center for Devices and Radiological Health and commended the FDA for doing what is best for all concerned under difficult circumstances. **Ms. Thornton** thanked Dr. Sugar for serving as Interim Chair and all new and returning panel members for their work.

Panel Chair Dr. Sugar adjourned the Open Session at 3:50 p.m.

I certify that I attended the Open Session of the Ophthalmic Devices Advisory Panel Meeting on November 30, 2001, and that this summary accurately reflects what transpired.

Sara M. Thornton
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.

Joel Sugar, M.D.
Interim Chair

Summary minutes prepared by
Aileen M. Moodie
Editorial Consultant

9821 Hollow Glen Pl.
Silver Spring, MD 20910