

SUMMARY MINUTES

OF THE

OPHTHALMIC DEVICES PANEL MEETING

ONE HUNDREDTH MEETING

November 8, 2000

OPEN SESSION

**Holiday Inn
Walker/Whetstone Rooms
Gaithersburg, MD**

OPHTHALMIC DEVICES PANEL MEETING

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PANEL PARTICIPANTS

Joel Sugar, M.D.	Chair
Arthur Bradley, Ph.D.	Voting Member
Michael R. Grimmett, M.D.	Voting Member
Janice M. Jurkus, O.D.	Voting Member
Alice Y. Matoba, M.D.	Voting Member
Jose S. Pulido, M.D.	Voting Member
Jayne S. Weiss, M.D.	Voting Member
Karen Bandeen-Roche, Ph.D.	Consultant, deputized to vote
Mark A. Bullimore, MCOptom, Ph.D.	Consultant, deputized to vote
Anne L. Coleman, M.D.	Consultant, deputized to vote*
Eve J. Higginbotham, M.D.	Consultant, deputized to vote*
Clifford A. Scott, O.D., M.P.H.	Consultant, deputized to vote
Diane K. Newman	Consumer Representative
Marcia S. Yaross, Ph.D.	Industry Representative

*Primary Reviewers for PMA P000026

FOOD AND DRUG ADMINISTRATION PARTICIPANTS

Sara M. Thornton	Panel Executive Secretary
Daniel G. Schultz, M.D.	Deputy Director for Clinical and Review Policy Office of Device Evaluation
A. Ralph Rosenthal, M.D.	Director, Division of Ophthalmic Devices

Jan C. Callaway	Microbiologist Diagnostic & Surgical Devices Branch
James F. Saviola, O.D.	Chief, Vitreoretinal and Extraocular Devices Branch Acting Chief, Ear, Nose and Throat Devices Branch
Donna R. Lochner	Chief Intraocular & Corneal Implants Branch
Bernard P. Lepri, O.D., M.S., M.Ed.	Optometrist Vitreoretinal & Extraocular Devices Branch
Gene Hilmantel, O.D., M.S.	Optometrist Vitreoretinal & Extraocular Devices Branch
Don Calogero, M.S.	Biomedical Engineer Intraocular and Corneal Implants Branch Team Leader for PMA P000026

SPONSOR REPRESENTATIVES

Steven L. Ziemba, M.S.
Senior Vice President, Regulatory Affairs, STAAR Surgical Company

Stephen Bylsma, M.D.
Assistant Professor of Ophthalmology, UCLA
Consultant to STAAR and Medical Monitor for AquaFlow IDE Study

Donald Sanders, M.D., Ph.D.
Consultant to STAAR Surgical Company

OPEN SESSION—NOVEMBER 8, 2000

Joel Sugar, M.D., Panel Chair, called the meeting to order at 8:30 a.m. **Sara M. Thornton, Panel Executive Secretary**, noted that this session was the 100th meeting of the Ophthalmic Devices Panel and thanked the panel for its many years of productive work. She introduced the new Panel Chair Dr. Joel Sugar and new panel voting members Arthur Bradley, Ph.D., Michael R. Grimmatt, M.D., and Jayne S. Weiss, M.D., observing that Eve J. Higginbotham, M.D., James P. McCulley, M.D., and Mark A. Bullimore, MCOptom, Ph.D., had finished their terms as voting members of the panel but would remain as panel consultants. Ms. Thornton asked the other panel members to introduce themselves and read the conflict of interest statement, noting that matters concerning Arthur Bradley, Ph.D., Eve J. Higginbotham, M.D., Janice M. Jurkus, O.D., and Clifford A. Scott, O.D., M.P.H., had been considered but deemed unrelated and their full participation allowed. She also read appointments to temporary voting status for Karen Bandeen-Roche, Ph.D., Mark A. Bullimore, MCOptom, Ph.D., Anne L. Coleman, M.D., Eve J. Higginbotham, M.D., and Clifford A. Scott, O.D., M.P.H.

OPEN PUBLIC HEARING

There were no requests to address the panel.

OPEN COMMITTEE DISCUSSION

Daniel G. Schultz, M.D, deputy director of Clinical and Review Policy in the Office of Device Evaluation, congratulated the panel on its 100th meeting, saying that it was conceivably the first panel to reach 100 meetings and thanking the panel for its dedication over the last 25 years. He noted

the accomplishments of past and present panel chairs and members in areas such as intraocular lenses, lasers for refractive surgery, classification of devices that were on the market before the Medical Devices Amendments Act of 1976, and with a wide variety of devices contributing to public health. Dr. Schultz presented letters of appreciation from FDA Commissioner, Jane Henney, and commemorative plaques to outgoing panel members Drs. Bullimore and Higginbotham. He also read Dr. Henney's letter of appreciation to former Panel Chair James P. McCulley, who was not present, noting that Dr. McCulley would receive a similar plaque.

Division Updates

A. Ralph Rosenthal, M.D., director of the Division of Ophthalmic Devices, told the panel that Dr. Morris Waxler, former chief of the Diagnostic and Surgical Devices Branch, has retired. Ms. Claudine Krawczyk, formerly a reviewer with the Division, has also left. Three new staff members have been added to the Division: Dr. Gene Hilmantel, optometrist and statistician, Dr. Dexiu Shi, vision scientist, and Dr. Jeffrey Toy, molecular biologist.

Jan C. Callaway, microbiologist, gave the update for the **Diagnostic and Surgical Devices Branch.** She noted that PMA P990078 for the Sunrise Hyperion LTK System had been approved on June 30, 2000, for use with temporary reduction of hyperopia in patients with +0.75 to +2.5 diopters of manifest refraction spherical equivalent, where the magnitude of correction with this treatment diminishes over time, with some patients retaining some or all of their refractive correction. She listed three PMA supplements that have been approved: P970053/S2 for the Nidek EC-5000 on April 14, 2000,

indicated for correction of myopia with astigmatism at specified ranges using laser in situ keratomileusis (LASIK); P970043/S7 for the Summit/Autonomous LADARVision on September 22, 2000, for use in correcting hyperopia, hyperopic astigmatism, and mixed astigmatism at specified ranges using LASIK; and P930016/S10 for the VISX STAR S2 & S3 Excimer Laser System for correction of hyperopia with astigmatism at specific ranges using photorefractive keratectomy. Five 510ks have been cleared: the K993153 Intralase 600C Laser Keratome on December 17, 1999; the K000327 VISX WaveScan Wavefront Analysis System on May 2, 2000; the K000637 Autonomous Custom Cornea Measuring Device on May 19, 2000; the K993154 ARC Laser for the Dodick Laser Phacoemulsification System on June 27, 2000; and the K991124 VisiJet Hydrokeratome on October 20, 2000.

James F. Saviola, O.D., chief of the Vitreoretinal and Extraocular Devices Branch, gave the branch update, noting a recently cleared 510k for Cantor & Silver Limited's ChromaGen lenses, which are tinted prescription contact lenses intended as an optical aid of people with red-green color vision deficiencies. He listed restrictions and limitations on these lenses, noting that the concept is not new; the FDA has determined the ChromaGen lenses are substantially equivalent to prescription contact lenses, and the manufacturer has conducted clinical studies to support the new indication for use. Dr. Saviola also stated that Alcon's Opti-Free EXPRESS Multi-Purpose Disinfecting Solution recently received two marketing clearances to modify their directions for use to eliminate the rubbing step during the cleaning of soft contact lenses.

Dr. Saviola also noted that two premarket approval applications (PMAs) have been approved for Scott Medical Products' Perfluoropropane (C3F8) gas used as a tamponade within the eye to place pressure on a detached retina. P900066/S003, approved on March 16, 2000, involved changes in the perfluoropropane process and manufacturing location. Special supplement P900066/S004 was approved as of September 5, 2000 to allow changes to the toxicity test protocol. Dr. Saviola noted that because this is a single manufacturer, the FDA is sensitive to potential supply problems that may develop and result in device shortages.

Ms. Donna R. Lochner, chief of the Intraocular and Corneal Implants Branch (ICIB), gave the branch update. She reported that PMA 990013 for Staar Surgical, Co.'s Collamer UV-Absorbing Posterior Chamber intraocular lens was approved on April 2, 2000. It was not brought to panel because it raised no new issues of safety or effectiveness. All PMAs that have been brought before the panel from the ICIB have received FDA final action. Ms. Lochner also reported that Ms. Ashley Boulware has been named FDA Engineer of the Year for 2001, a highly competitive award that recognizes her expertise in the biomaterials and optical areas.

**PMA P000026—STAAR SURGICAL COMPANY'S AQUAFLOW COLLAGEN
GLAUCOMA DRAINAGE DEVICE**

Sponsor Presentation

Mr. Steven L. Ziemba, M.S., vice president for regulatory affairs at STAAR Surgical Company, introduced the sponsor team and the AquaFlow Collagen Glaucoma Drainage Device,

which is indicated for the reduction of intraocular pressure (IOP) in patients with primary open angle glaucoma (POAG) that is uncontrolled on maximum medication.

Stephen Bylsma, M.D., assistant professor of ophthalmology at UCLA and consultant to STAAR Surgical Company, gave an overview of treatment options for POAG. He noted that trabeculectomy is the standard of care for lowering IOP in POAG patients who have failed on maximally tolerated medication, but presents the dual concerns of overfiltration and underfiltration that must be avoided. AquaFlow solutions to these problems are to avoid overfiltration by maintaining resistance through a nonpenetrating deep sclerectomy and to avoid underfiltration by preventing fibrosis through slow resorption, with no use of antimetabolites and minimal inflammation, and by allowing a late YAG goniotomy to lower IOP if needed. Dr. Bylsma showed a schematic of the procedure and a video in which he explained the implant technique. He noted that the implant is completely absorbed by 18 months and that the typical postoperative course shows large, diffuse, quiet blebs, recovery of baseline visual acuity in week 1-2, and no IOP medications. Full recovery is achieved within one to two weeks.

Donald Sanders, M.D., Ph.D., consultant to STAAR Surgical Company, described the AquaFlow U.S. study. He observed that the original design was a randomized, prospective comparison of deep sclerectomy with collagen implant (DSCI) to trabeculectomy with antimetabolites, but the FDA rejected this design because antimetabolites are not labeled for use in trabeculectomy surgery. The sponsors' glaucoma consultants rejected a comparison to trabeculectomy without antimetabolites saying that was not the current standard of care, so it was agreed that the design would be a comparison of

DSCI to nonrandomized historical trabeculectomy controls. Sponsors and FDA agreed that the PMA would be submitted with more than 100 cases at the one-year postoperative point. The rationale for this decision was that the AquaFlow device was absorbed by one year postoperatively and therefore poses no late safety concern, with 100 cases being sufficient to document efficacy within acceptable statistical limits.

The trial was conducted at nine investigational sites with at least 92% accountability at all points and 97% accountability at 12 months. PMA cohort demographics based on 194 eyes with POAG, at a mean age of 67, of whom the majority were Caucasian and about half were female. Dr. Sanders stated that safety outcomes showed a very low rate of adverse events and only two surgical complications, both of which were procedurally related and not a result of device implantation. The overwhelming majority of complications reported at less than one week after DSCI were due to the normal healing process, and the only complications reported at the six month visit or later were one case of hyphema, one iris prolapse, and one progression of preexisting cataracts. Loss of best spectacle corrected visual acuity (BSCVA) of more than two lines occurred largely because of cataract progression or worsening macular degeneration.

Dr. Sanders observed that effectiveness outcomes showed a highly statistically significant decrease in IOP from preoperative to 12-month postoperative outcome in the PMA cohort, as well as a highly significant drop in the mean number of glaucoma medications. The PMA cohort achieved complete success (as defined by IOP of less than or equal to 21 mm HG and no medications) for

roughly 70% at 12 months, and overall success (as defined by the same IOP with medications) for 90%. Failure rates were in the 10 to 12% range.

The sponsors also compared these success outcomes of the AquaFlow study (with no antimetabolites therapy) to trabeculectomy peer-reviewed literature with and without antimetabolites therapy. Using this criteria, success rates of patients achieving IOP of less than or equal to 21 mm Hg and no glaucoma medications at 12 months reached 72 percent. Overall success rates at 12 months (IOP of less than or equal to 21 mm Hg plus or minus glaucoma medications) reached 90%. Overall success rates at 12 months in comparison to trabeculectomy with antimetabolites again reached 90%. The PMA cohort showed a low rate of needing additional filtering surgery, in comparison to trabeculectomy without and with antimetabolites.

Dr. Sanders also discussed data from peer-reviewed literature on DSCI. He cited a study by Sanchez et al. that showed the Aqua Flow device enhances the outcome of deep sclerectomy alone, a point not addressed in the original PMA. This prospective study using matched controls on 168 eyes with half having DSCI and roughly half DS with no collagen implant found that the implant allowed better long term complete and overall success, lower postoperative need for glaucoma medication, and lower risk for late bleb fibrosis.

Studies on long-term efficacy of the device by Mermoud et al. on 88 eyes comparing DSCI to a matched control group with trabeculectomy showed that the success rate of DSCI may be compared to that of trabeculectomy with fewer complications. A study by Karlen et al. on 100 consecutive patients

with uncontrolled primary and secondary glaucoma treated with DSCI found that DSCI appears to provide reasonable control of IOP with few immediate postoperative complications. A prospective, nonrandomized study by Shaarawy et al. on five-year results of deep sclerectomy with collagen implant showed efficacy was sustained through 60 months at least. Comparison studies by Mermoud et al. looking at Nd:YAG goniopuncture after DSCI found that goniopuncture offers efficient, safe, and successful treatment for low filtration. Dr. Sanders concluded that published and unpublished reports all support safety and effectiveness of DSCI with AquaFlow, with a decrease in IOP and glaucoma medications and complete and overall success all comparable or better than trabeculectomy. DSCI effectiveness outcomes are stable through five years, with BSCVA virtually unaffected. Short- and long-term complications are significantly lower than trabeculectomy, and DSCI plus goniopuncture in a two-step approach offers a safe and stable decrease in IOP.

Panel questions to the sponsors concerned patient demographics, particularly whether there were statistics on non-Caucasian groups; which medications were used to lower IOP; the total number of surgeons in the literature review, and what the regulatory statutes were involving comparison of the procedure with or without the implant. Dr. Rosenthal clarified that the regulatory burden is to show that the device has reasonable safety and efficacy, not whether the implant adds value to the procedure. Other questions involved the sterilization of the device, the learning curve, and the postoperative drug regimen used.

FDA Presentation

Ms. Lochner noted valid evidence of safety and efficacy does not have to consist of controlled studies, and that while it is conventional to have a control arm, the IOL historical control grid can be used instead. She noted that this was the first implant reviewed for this indication, and that the sponsor was not required to demonstrate substantial equivalence to another device. Ms. Lochner thanked the FDA review team for its work.

Mr. Don Calogero gave the device description and introduced the FDA review team.

Dr. Bernard Lepri described the device, noting that the sponsors had presented numerous studies regarding the effectiveness of anterior sclerectomy both with and without the AquaFlow device, which facilitates the non-penetrating sclerectomy by maintaining the subscleral space created by the surgical procedure itself. Both nonpenetrating anterior sclerectomy and trabeculectomy are second-line therapies for glaucoma after failure to achieve IOP control with medication. Sponsors conducted a nonrandomized clinical trial using the results reported for trabeculectomy in the ophthalmic literature for comparison, using outcomes for trabeculectomy performed both with and without the use of anti-metabolites. The study objective was to show safety and effectiveness of the AquaFlow device, not of deep sclerectomy per se.

Dr. Lepri noted that 12-month accountability was achieved for 97.2% of the available cohort. No device-related adverse events were reported. Those complications that did occur were in the immediate postoperative period and related to the anterior sclerectomy. After the one-week

postoperative period, the complication rates were very low. Because the device is absorbed in the six- to nine-month postoperative interval, no late device-related complications are anticipated.

Ultrasound biomicroscopic photographs verify the absorption of the AquaFlow and presence of a subscleral space to facilitate the outflow of aqueous from the Schlemms' canal. Because UBM is not practical to perform at all postoperative visits, POAG must be evaluated by conventional clinical endpoints such as decrease in IOP and reduction in glaucoma medication. For the definitions of complete and overall success, with or without medication, the sponsor presented postoperative IOP trabeculectomy data of varying levels for comparison to those achieved via nonpenetrating sclerectomy with the AquaFlow. Additionally, the sponsor presented data regarding the decrease in the use of medication after sclerectomy with the use of the device, clinically significant changes in IOP from perioperative levels, and so forth. Dr. Lepri added that sponsors and others have noted that the postoperative IOP lowering medication regimen was not standardized, which may have affected the reported success rates.

There were no questions from the panel to the FDA representatives, and sponsor representatives had nothing further to add to the FDA review.

Primary Panel Reviews

Dr. Higginbotham gave the first panel review. She reviewed the device description, noting that the device is a space maintainer up to nine months following placement.

Regarding the clinical study, she noted that the nine-center, nonrandomized, prospective trial focused on a largely Caucasian population of more than 70 years of age, an important point because this population can do well with simple trabeculectomy. She recommended that labeling note that none of the eyes had undergone previous filtration surgery, which would influence efficacy, and that Fornix-based versus limbal-based conjunctival periotomy was not specified, which would influence complication rate. A stepped regimen for adding back medications was not specified, which would influence efficacy. Dr. Higginbotham urged that greater follow-up be done on more patients, given that the percentage of the original cohort followed diminished over time and that the implant dissolves after nine months. Longer follow-up is also needed to show whether the device imparts any enhanced level of success, given that a high success rate would ordinarily be expected with this population.

On safety, Dr. Higginbotham observed that complications noted are largely related to trabeculectomy in a predominantly elderly population. She concluded that the AquaFlow Collagen Glaucoma Drainage Device is safe, but urged longer follow-up to show that the device adds to the effectiveness of filtration surgery.

In answer to a question from another panel member who asked whether deep sclerectomy with the collagen implant lowers IOP, Dr. Higginbotham replied that it appears to, but the effect after nine to twelve months is unknown.

Anne L. Coleman, M.D., Ph.D., gave the second panel review. After describing the device and the U.S. clinical trial, Dr. Coleman took issue with the sponsors' definition of procedure-related

adverse events and stated that she would class all procedure-related and postoperative complications as adverse events, saying that it would have been helpful to have the confidence intervals calculated for all of the event rates. She also commented that it would have been helpful for the sponsor to use Kaplan-Meier life table analyses in the calculation of success rates because that analysis takes into account subjects who are lost to follow-up or who have died, in addition to those who succeeded or failed.

Dr. Coleman recommended that the labeling note that the device was designed to be used in successful nonpenetrating deep sclerectomies. It should give greater descriptiveness regarding the type of open angle glaucoma because the U.S. trial did not include uveitic, neovascular, pseudophakic, aphakic, or congenital glaucoma. Dr. Coleman recommended including a number of changes to the labeling based on adverse events and complications and suggested reporting goniopuncture as an additional filtering surgery, with the note that those subjects tended to have more postoperative medications. She also recommended more information on sterilization of the device. Dr. Coleman considered the PMA approvable with the conditions that the indication and labeling were changed as recommended because the PMA did indicate that the device is as safe and effective as trabeculectomies, the gold standard for glaucoma surgery.

General comments from the panel stressed the need to address when traditional trabeculectomy should be chosen over sclerectomy. There was also some discomfort expressed with the limited number of surgeons and the length of follow-up in the trial and whether there would be a need for a repeat procedure, given the lack of long-term results.

FDA Questions

1) Does the indication as stated adequately describe the mode of action and the target population for treatment?

The panel recommended that the indication should read, “The AquaFlow device is indicated for the reduction of intraocular pressure in patients with primary open-angle glaucoma who have had no previous conjunctival surgery.”

2) Does the panel have any additional labeling recommendations?

Additional labeling issues from the panel were as follows:

There were not sufficient long-term follow-up data to make recommendations beyond 12 months.

Data were not available on uveitic, neovascular, pseudophakic, aphakic, or congenital glaucoma, all of which are types of open angle glaucoma.

The possible need for goniotomy should be noted.

The clinical trial did not examine the advantage of deep sclerectomy alone.

Fornix-based flaps were primarily used in the procedure.

There is a learning curve for the procedure.

The FDA should not promote the use of the term “minimally invasive” to describe such procedures.

Repetition of surgery with the device in the same site has not been studied.

Success rate without medication should be discussed.

The frequency of use of postoperative steroids should be examined and a statement added that the dosage and frequency and duration of postoperative steroids have not been delineated.

3) Do the data presented support reasonable assurance of safety and effectiveness for the indication?

The panel felt that the question had been addressed in the previous discussion in a global sense and had nothing more to add.

OPEN PUBLIC HEARING

There were no requests to speak.

FDA CLOSING COMMENTS

Dr. Rosenthal asked the panel to comment on whether postmarket follow-up in this cohort was indicated. Follow-up of 70 to 80% of the current cohort was suggested.

SPONSOR CLOSING COMMENTS

The sponsors thanked the panel for its remarks.

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) That the indication for use be revised to say that this is an adjunctive device indicated for use with primary open-angle glaucoma where IOP remains uncontrolled and where patients have

undergone a successful nonpenetrating deep sclerectomy and no other prior conjunctival surgery. This condition carried with one opposed.

2) That labeling be revised to state

That effectiveness data on a non-Caucasian population are limited.

That there is no conclusive demonstration that the adjunct device produces an end result better than deep sclerectomy alone.

That long-term follow-up data are limited.

That a secondary or repeat procedure has not been evaluated.

That the device has not been thoroughly evaluated in glaucomas other than POAG.

That a proportion of patients will need goniopuncture.

That a learning curve is associated with the device.

That Fornix base flaps were primarily studied.

That the postoperative frequency and duration of steroid use were not delineated in the study.

That the efficacy of the device may depend on age and gender of the subject group (Dr.

Rosenthal was asked to work with statisticians to work out wording on race, gender, and age issues.)

That there should be specified outcome data, including success rate with and without medications.

The above condition carried.

- 3) That there should be continued follow-up of a reasonable number of the original cohort for up to two years to ensure effectiveness. This motion carried.

The motion to recommend the PMA as approvable subject to the above conditions was carried with one opposed.

DISCUSSION OF A POSTMARKETING APPROVAL STUDY FOR 30-DAY CONTINUOUS WEAR LENSES

Dr. Saviola thanked Dr. Rosalie Bright of the Office of Statistics for her work in preparing for the meeting. He reviewed the history of extended wear lenses, noting that in the early 1980s the FDA approved some contact lenses for up to 30 days. Increasing reports of problems with corneal ulcers prompted FDA to recommend that continuous wear be limited to a maximum of 7 days. New materials are now available that make it likely that 30 day continuous wear lenses will be submitted for approval. The reference for such lenses would be the literature of the last 13 years for all extended wear lenses, not just specific PMAs.

Dr. Lepri added that there are concerns about longer wear lenses and increased safety risks, particularly the development of corneal ulcers. The incidence of such ulcers is probably too low to address in a PMA, so it was thought advisable to address them in a postapproval study, for which panel input was sought. The FDA is seeking a study design that will be least burdensome yet provide a reasonable assurance of safety.

Gene Hilmantel, O.D., M.S. stated that new contact lens materials with much higher oxygen transmission provide have the potential for safer continuous wear for longer periods of time.

However, the incidence of corneal ulcers remains a safety concern. Because the incidence of ulcers is too low to reliably determine the risk in a reasonable PMA study, the FDA suggests that the best way to address this concern is to require a postmarketing approval study of the risk posed by a 30-day continuous wear lens.

The FDA wants the panel to make a recommendation as to what ulcer rate should be used as a maximum acceptable risk for statistical testing. In determining the maximum acceptable risk, the panel should consider what has been done in the past. In a 1989 study Oliver Schein looked at relative ulcer risk posed by extended wear versus daily wear. He found that the risk increased with each additional night of wear. Using this data, over a decade ago the FDA recommended limiting continuous wear to a maximum of 7 days. From the 1989 Schein data, it seemed that the FDA considered a relative risk for extended wear of about 12-15 (compared to daily wear) as unacceptable. Eugene Poggio's 1989 study found that the incidence of ulcers was 4 per 10,000 in daily wear and 20 per 10,000 in extended wear. Assuming that 15 times the risk of daily wear is unacceptable, this would mean that an ulcer incidence of 60 per 10,000 is too much risk. 60 per 10,000 is about two to four times the risk of 7-day extended wear lenses. It was pointed out that these are only annual ulcer rates and that the panel should consider lifetime ulcer risks. Lifetime ulcer risk was displayed as a function of annual ulcer rate and number of years wearing contacts. It

was noted that at 20 years, the lifetime risk would range from 1% for an annual rate of 4/10,000 to 12% for an annual rate of 60 per 10,000. However, about 90% of these ulcers are not associated with vision loss.

The FDA therefore asked what ulcer rate the panel would recommend as the maximum acceptable risk to be used as an upper limit for statistical testing. Another issue involved the type of study to be recommended—a case-control study, or a cohort study. Dr. Hilmantel outlined advantages of a case-control study: (1) One can assess relative risk of different actual wearing schedules, (2) It is good for the study of rare diseases, (3) It uses a small number of subjects making it relatively inexpensive, (4) The relative risk of different hygiene practices can be assessed, and (5) It provides a “real-world” environment. Disadvantages of a case-control study are that it requires a waiting period until 30-day lenses have sufficient market share and it only assesses relative risk, not actual incidence of ulcers. If the ulcer rate for seven-day lenses has decreased since 1989, this could be a problem. It also generally produces large confidence intervals or else requires a very large numbers of ulcers.

A related question for the panel concerned whether there will be difficulty in getting enough extended wear ulcer cases to do an effective case-control study, since half of all contact lens ulcers are from daily wear, and now treatment is more widely available from nonspecialists. Tables were given to show the relationship between maximum acceptable risk and required sample size.

Statistical power is a key measure of confidence in product safety, and power and sample size are strongly related. There is an interplay between market penetration and sensitivity and power of the statistical test. The FDA asked what statistical power the panel would recommend to ensure confidence in product safety and whether a case-control study should be delayed until there is greater penetration of the market, to achieve greater sensitivity and power.

An alternative way to assess risk would be following a large cohort of 30-day wearers. This could be done by requiring a large number of practitioners to fill out a follow-up questionnaire after one year of experience. This approach might yield results within about two years of approval and could assess the actual incidence of ulcers and other complications. However, it uses selected patients and practitioners in a relatively controlled follow-up environment. The cost may also be higher. It was pointed out that the clinical setting for the implementation of a cohort study could influence the retention of patients in the study and might bias the finding. The panel was asked to consider what type of clinical setting should be recommended.

The FDA asked the panel what type of study they would recommend: a case-control study, a large cohort study, or some combination of the two. The panel was also asked to recommend a definition of study endpoints, as there has been considerable ambiguity in the definition of a clinically significant ulcer.

Panel Discussion

The panel discussed whether applying Bayes Theorem would help to calculate the incidence rate in particular group, provided that the population incidence and relative risk are available. It was noted, that the lifetime ulcer rate assumes all are equally disposed to ulcers. One member suggested a more sophisticated model could include the factors that increase the likelihood of risk, such as hygiene, smoking, etc., but it was noted that the most important factor by far is the number of nights the lenses are worn. It was postulated that the wearers of 30-day lenses might be more likely to break protocol, which could be studied mathematically. It was also noted that the eyes of 20-year contact wearers are different from those of new wearers, which must be factored in.

The panel discussed at length whether the comparison for 30-day extended wear lenses should be seven-day wear or daily wear. There was some confusion over whether comparison should be made to seven-day lenses with new or existing materials, with concern that the benchmark had become a moving target.

Specific FDA Questions

1) What ulcer rate does the panel think we should use as the maximum acceptable risk?

The panel discussed whether the comparator should be seven-day lenses or daily wear lenses and whether new materials should be compared to old. There was discussion of the risk/benefit ratio and whether there is enough additional benefit in 30-day extended wear lenses to justify any higher risk than that with seven-day lenses. Possible benefits to justify a higher risk were given as cost or

preference for the extended wear lens over refractive surgery. Other possible benefits included use with the elderly or handicapped. One member commented that the benchmark posed as the upper confidence limit is not higher than acceptable, but the problem is that the currently acceptable level for seven-day wear may not be appropriate for newer technology. One member suggested that new contact lenses for 30 day wear should show equivalence to seven-day lenses and two times the seven-day ulcer rate as the upper bound, but there was no unanimity of opinion. The sense of the panel as summarized by Dr. Saviola was to minimize any increase in risk and the lower the number the better.

2) Does the panel feel there would be difficulty in getting enough extended wear ulcer cases for an effective case-control study?

The panel discussed the fact that many ulcer cases are no longer referred to tertiary centers for treatment but are routinely treated by nonspecialists and not reported. It was also noted that the benchmark is tied to the definition of an ulcer, so the definition must be carefully crafted, despite the vagueness of the original definition used in the Schein study. A couple of the panel members felt that, based on their experience, there would be no difficulty in getting enough extended wear ulcers for an effective study.

3) What statistical power would the panel recommend to ensure confidence in the result?

The statistical power should be higher than a research study to discriminate between the two groups and the bar should be set higher than 80%.

4) In order to achieve greater sensitivity and power would the panel recommend waiting until 30% market penetration is achieved or accumulating cases over a two-year period or both?

The panel suggested giving the sponsor a choice, noting that to wait for 30% market penetration would be difficult. A speedier method would be case accumulation, but it was noted that an exact time limit was not needed. The study should be done once an appropriate number of cases have accumulated. Sales of units should also be reviewed, to be sure the consumers are actually wearing the lenses on a 30-day basis.

5) What type of clinical setting would the panel recommend for implementation of postapproval cohort study?

The panel urged that all of the suggested settings be used, with strong direction from the FDA to get a sampling across the board. Broad participation should be encouraged through whatever means are necessary, and the decision not left to the sponsor.

6) What type of study would the panel recommend? A case control study or a cohort study or both?

Several members of the panel recommended both. The cohort study is good to estimate incidence rate, but a case control study is good if there are participation biases. The Industry Representative recommended an early study to rule out disaster but thought that an additional later study was too burdensome. One member argued for a case control study rather than waiting for a cohort study on

the grounds of ease of accumulation, but another thought that the case control approach does not capture the incidence level. He urged that any case control study must be extremely rigorously controlled. Dr. Rosenthal asked if the burden of a cohort study is necessary when all that is needed is relative risk. One member noted that if the comparator is seven-day wear, relative risk is all that is necessary, which can be achieved with case control studies. He recommended reviewing the literature from international studies because variability in definition and reporting time made a true incidence rate highly dubious. The panel again noted that if the new materials seven-day lens is being compared to the new material 30-day lens, the issue is further confused by introduction of a moving target.

7) How would the panel define the endpoints we are interested in the study?

The panel thought the more the original definition is changed, the less the historical benchmark means, although they noted that endpoints in the Schein study were very loosely defined. One suggestion was that to be considered an ulcer, an infiltrate should have the clinical appearance of microbial keratitis but not necessarily require a culture. Another suggestion was to concentrate on visual acuity loss and catch visually significant ulcers, although this would be a stringent standard. Yet another was a patient poll for any eye condition in which they were required to stop wearing lenses and have antibiotic treatment, although this was rejected as too broad. The use of standard instruments to provide quality of life measures and benefit of extended wear in a pre and postmarket analysis was also mentioned.

Other Issues

The FDA thanked the panel, saying that they need a postmarket protocol because they expect a submission in six to nine months.

Open Public Hearing

Peter Mathers, counsel to the Contact Lens Institute thanked the panel and the FDA for a helpful exchange, noting the complexity of these issues.

Industry Representative Marcia Yaross asked if the guidance being developed would go through Good Guidance Practice procedures. The FDA representatives replied that after drafting and level one review, it would go through the customary procedures.

Panel Comments

There were no additional remarks.

Executive Secretary Sara Thornton reminded the panel that the January 11-12 meeting had been canceled and asked them to check the status of the March panel meeting on the web. She thanked the panel members, especially Diane Newman, who was substituting for regular Consumer Representative Lynn Morris.

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 8, 2000, and that this summary accurately reflects what transpired.

_____/S/_____
Sara M. Thornton
Executive Secretary

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

_____/S/_____
Joel Sugar, M.D.
Chair

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