SUMMARY MINUTES

MEDICAL DEVICES ADVISORY COMMITTEE

OPTHALMIC DEVICES PANEL

111TH MEETING

June 10, 2008

Hilton Washington D.C. North

Gaithersburg, Maryland

Ophthalmic Devices Panel Meeting
June 10, 2008
Attendees

Chairperson (Acting):
Neil M. Bressler, M.D.
Wilmer Eye Institute

Voting Members:
Stephen A. Burns, Ph.D.
Indiana University

Timothy B. Edrington, O.D.
Southern California College of Optometry

Janine A. Smith, M.D.
National Eye Institute

Consultants (Deputized to vote):
Donald G. Ahearn, Ph.D.
Georgia State University

Timothy T. McMahon, O.D.
University of Illinois at Chicago

William D. Mathers, M.D.
Oregon Health Sciences University

Alice Y. Matoba, M.D.
Baylor College of Medicine

Thomas W. Raasch, O.D., Ph.D.
Ohio State University

Loretta B. Szczotka-Flynn, O.D., M.S.
Case Western Reserve University

Consumer Representative:
Richard T. Bunner
Private Public Health Consultant

Industry Representative:
Barbara A. Niksch
Visiogen, Inc.

Executive Secretary:
Karen F. Warburton, M.H.S.

FDA Representative:
Malvina B. Eydelman, M.D.

CALL TO ORDER

Dr. Bressler called the meeting to order at 8:00 a.m. The purpose of the meeting was to discuss general issues concerning post-market experience with various contact lens care products. **Executive Secretary Warburton read** the conflict of interest (COI) statement. All members and consultants were found to be in compliance, and waivers were issued for Drs. Ahearn, McMahon, and Szczotka-Flynn. **Dr. Eydelman** presented a plaque and letter of appreciation to Dr. Mathers in recognition of his service to the Panel.

DIVISION UPDATE

Dr. Eydelman gave an update on personnel in the division. There have been three departures and seventeen additions since the July 2006 meeting. The additions are Dr. Denise Hampton, Andrew Yang, Dr. Mridulika Virmani, Kwame Ulmer, Dr. Shu-Chen Peng, Dr. Kimberly Brown Smith, Dr. Anjum Khan, Shelley Buchen, Dr. Sam Dahr, Dr. Alex Beylin, Sushma Nair, Dr. Daniel Clupper, Dr. Lee Kramm, Dr. Molly Ghosh, Anna Postell, Quynh Hoang, and Rahul Ram.

Dr. Kesia Y. Alexander, Chief of the Intraocular and Corneal Implants Branch, gave an update on her branch. PMA P060011, the Rayner C-Flex Intraocular Lens Model 570C was approved on May 3, 2007. It is indicated for primary implanntation for visual correction of aphakia in adults in whom a cararactous lens has been removed by phaxoemulsification. The April meeting to reassess PMA P050034, VisionCare's Implatable Miniature Telescope, was postponed and FDA is working with the sponsor on outstanding issues. There has been an influx of Toxic Anterior Segment Syndrome (TASS) cases being reported. In response, an inter-center collaborative program has been established to ensure relevant reporting of device-related issues, provide a trend analysis, allow for testing of suspected devices, offer support for potential compliance action, and facilitate prompt communication with the ophthalmic community. FDA has joined with the American Academy of Opthalmology to create a TASS Communication Task Force, and MedWatch has been modified to aid in capturing important information. ASCRs and AAO have links to the form on their websites.

Kwame O. Ulmer reported from the Diagnostic and Surgical Devices Branch. FDA has approved the following significant PMAs since the last meeting: P020050, Supplement 4, the WaveLight Allegreto Wave Excimer Laser System for use in conjunction with the WaveLight Allegro Analyzer for reduction of myopia or myopia with astigmatism up to 7 diopters; P060004, the Carl Zeiss MEL 80 Excimer Laser System for use in primary LASIK treatment for reduction of myopia of less than or equal to 7 diopters; P970053, Supplement 9, the NIDEK EC-5000 Excimer Laser System for reduction of hyperopia from 0.5 to 5 diopters for patients with documented stability of manifest refraction; and P930016, Supplement 25, the VISX STAR S4IR Excimer Laser System and WaveScan System for monovision. AMO VISX agreed to perform a post-approval study for monovision to estimate the proportion of monovision patients who experience visual disturbances that affect quality of life.

Quynh T. Hoang reported from the Vitreoretinal and Extraocular Devices Branch. One PMA has been approved: P050031, Paragon Science's Paragon Z CRT (tisilform A) Rigid Gas Permeable Contact Lens for Corneal Refractive Therapy. A postmarket study is being conducted under the authority of Section 522 for patients under 18 years of age. The branch has also been responding to the *Fusarium* and *Acanthamoeba* keratitis outbreaks identified by the CDC.

Dr. Danica Marinac-Dabic reported from the Epidemiology Branch, giving an update on PAS (Post-Approval Studies) and post-market surveillance. PAS are made as conditions of approval of PMAs. Post-market surveillance studies are ordered after a device is on the market. CDRH has enhanced the PAS Program to enhance rigor, maintain accountability, build an information management system, bridge pre- and post-market knowledge, and increase transparency. Accomplishments have been made in oversight, tracking, review process, guidance documents, web posting, post-market advisory panel updates, and building public health partnerships. An automated system for tracking PAS commitments was developed in 2005. An epidemiologist has been added to each PMA review team. The teams work with the sponsor to help design the studies pre-market to have a protocol finalized at the time of PMA approval. The Post-Market Review Team remains engaged throughout.

The branch issued guidance documents to industry and staff on PAS expectations in 2006 and 2007. The PAS webpage went online in 2007. It provides the reporting status and updates for all studies initiated post-2005. Proprietary information is protected and not posted on the site.

The branch now provides updates on PAS to the Panel, and specific updates can be given to the Panel jointly by the sponsor and the Branch. All stakeholders are being included in the PAS process. There was a conference on this in 2007 and there will be conferences in 2008 and 2009.

Since 2005, there have been 15 PMAs or Panel Track Supplements approved. Four PAS were requested. All of the studies are observational. For two studies, report is pending but not yet due. For one, the report is on time. For one, it is overdue but received. The vision for the program is to have good science with specific questions the sponsor can address and for all stakeholders to be kept apprised. Burden, workload, fairness, and added value are discussed in a collaborative manner by all stakeholders. This is put in the context of askiing the right post-market questions. She welcomed input from the Panel on improving the transformation of the program.

OPEN PUBLIC HEARING

Dr. Bressler called the open public hearing to order, encouraging speakers to disclose any relevant financial interests.

Thomas Moore, an attorney who represents patients with corneal infections, related his clients' concerns. He said the increase in Acanthamoeba infections was due to the use of multi-purpose solutions (MPS) rather than hydrogen peroxide and heat. MPS rely on PHMB in concentrations too low to be effective against Acanthamoeba. Neither ISO nor FDA require testing against Acanthamoeba. Though the manufacturers have claimed that

the testing could not be done, the testing is done internally and is the basis for claims of effectiveness in advertising. He cited literature that showed variability in the effectiveness of PHMB-based solutions. An increase in cases coincided with the 2003 launch of Complete MoisturePlus. Despite outbreaks and recalls, testing and labeling standards have not changed. Though patients applaud the meeting, there is distrust due to past lack of transparency and a perception that FDA's relationship to the manufacturers is closer than to the public. He said FDA did not respond to FOIA (Freedom of Information Act) requests in a timely manner and has deemed briefing documents as confidential. Transparency in regulation and the inclusion of patients as important stakeholders will prevent negative perceptions.

Dr. William Ehlers, a corneal specialist and past president to CLAO (Contact Lens Association of Ophthalmologists), spoke on behalf of the American Academy of Ophthalmology, the Contact Lens Association of Ophthalmologists, the Cornea Society, and the American Society of Cataract and Refractive Surgery, organizations that have been collaborating to develop recommendations to the FDA and consumers on contact lens safety. He said he had no financial interests to disclose. He presented the organizations' recommendations to the consumers. First was to wash hands before handling contact lenses. Second, wearers should avoid contact with water, either recreational contact while wearing them or contact by rinsing the lenses in water. Lens cases, like lenses, should be washed in lens care solution, not water. Appropriate solutions should always be used. All wearers should follow the wear and replacement schedules prescribed by the physician, and those guidelines should be made clear by the manufacturers and eye care professionals.

Patients should rub their lenses during the cleaning process, rinse the lenses, then soak them. The no-rub approach is inferior. The case should be rinsed with solution and air-dried before reuse, and it should be replaced every three months. Solutions must be handled with care and not transferred. When storing lenses, patients should consult instructions for re-disinfection guidelines. Daily disposable contact lenses are the safest type of soft lens, and rigid gas permeable lenses are safer than soft lenses. Patients should understand the risks associated with extended wear.

Patients should see an ophthalmologist immediately upon contracting an eye infection and should know the symptoms of lens problems. It is important to have regular examinations with eye care professionals. The practice of passive verification by third-party sellers leads to inappropriate prescriptions and complications. He said industry, researchers, FDA and eye care professionals must work together to ensure safe contact lens wear.

Dr. Elmer Tu, a cornea specialist, spoke for The American Academy of Ophthalmology, The American Society of Cataract and Refractive Surgery, Contact Lens Association of Ophthalmologists, and The Cornea Society. He disclosed honoraria and travel expenses received from Allergan and Alcon for unrelated educational activities. He noted that rates of microbial keratitis have not substantially declined, despite the evolution of disinfection systems. Elements of infection risk include the disinfection regimen, extended wear, reduced tear exchange, environmental factors, and poor hygiene. Research into all factors is required. He recommended discard dates on lens care

products, especially related to efficacy once the products are opened; research to verify the duration of safe extended storage of lenses after a single disinfection; and research on the biocompatibility of solutions and lenses.

He discussed the recalls associated with Fusarium and Acanthamoeba infections. The 2005-6 outbreak was associated with the ReNu with MoistureLoc solutions. However, the solution performed well in preclinical testing. Research suggests that the solution is effective in optimal use but not in common consumer use, since non-compliance is common. He recommended that preclinical testing include more real-world scenarios. Each change in product formulation should be subject to similar testing. The Acanthamoeba keratitis (AK) outbreak was associated with AMO's Complete MoisturePlus, though only 50 percent of infected patients used the product. Recall of the solution has not resulted in a decline in cases. Most previous outbreaks have been related to water involved in lens hygene. He recommended that testing requirements ensure effectiveness against a diverse and representative set of organisms, that testing protocols be standardized and validated, that testing include a spectrum of clinical isolates selected for virulence, and monitoring of infections.

Thomas Henteleff, counsel to the Contact Lens Institute (CLI), introduced **Dr. Glenn Davies**, a Bausch & Lomb employee representing CLI, an association of manufacturers. CLI supports enhanced testing requirements for lens care products to ensure safety and effectiveness and has worked with FDA to develop them. Lens care products have Class II guidance controls. CLI opposes collection of data in the absence of sound scientific methods and appropriate criteria. He reviewed CLI's ongoing efforts. CLI and FDA developed a protocol to assess MPS efficacy, which is being evaluated. CLI is working with ANSI and ISO to develop standards on disinfection efficacy, preparation of test samples for cytotoxicity evaluation, the kinetics of preservative uptake and release by lenses, and lens storage cases. CLI agrees that Acanthamoeba testing is appropriate to safety and efficacy evaluation, but there must be standardized, validated methods.

CLI members have eliminated water from all care regimens and warned in labeling about water-related activities. Care product compatibility may differ between silicone hydrogel and conventional hydrogel lenses, so testing is warranted. Testing should consider existing and evolving materials. CLI sorts silicone hydrogel lenses into four distinct groups.

CLI is developing a user-friendly caution statement to communicate the importance of patient compliance. CLI recommends that the statement be standardized and appear prominently and that an expanded statement be included as an insert. Innovation in contact lenses and care products should not be impeded by class labeling limitations. CLI members have deemphasized no-rub directions on packaging, and no-rub products include directions for use in a rub regimen. Evidence of safety and effectiveness of the recommended regimen was included in the 510k clearance process. CLI supports FDA's development of SightNet. He emphasized CLI's willingness to participate in developing enhancements to the Class II controls. Any test requirements should be evidence-based and administered uniformly.

Dr. Arthur Epstein, a consultant for Alcon Laboratories, noted that contact lenses, like all medical devices, present a risk that is balanced by the benefit. It is important to take

the opportunity to learn about the devices. The first problem is that patient compliance has been poor. Industry efforts to deal with compliance have not been successful, even during times of outbreaks and intense media attention. CDC studies of outbreaks showed no single hygiene practice associated with disease but showed that sub-optimal practices are common. Industry has responded to emphasize lens care in package labeling.

He recommended that testing and labeling reflect real-world challenges and patterns of use. Standards should reflect collaboration among FDA, ISO, ANSI, industry, and the eye care community. Testing for Acanthamoeba disinfection should be adopted, but only with validated standards. Testing should include traditional hydrogel lenses and silicone hydrogel lenses, recognizing the differing chemistry of the lenses and evolution of the technology. Corneal staining is a valuable tool in understanding the impact of the lens and product on the patient. Labeling should be science-based and product-specific. Class labeling will stifle innovation and mandate steps unnecessary for the safe and effective use of the product. Promotional claims should be removed from the front panel. Practitioners should reinforce compliance.

Dr. Doyle Stulting disclosed having consulted for many companies and having received traveling expenses from AMO, but he spoke on his own behalf. During the Fusarium keratitis outbreak, he examined patients with contact lens-related ulcers and obtained environmental specimens. His experience gave him insight into lens care practices and complications of lens wear. Care practices are often inconsistent with labeling. Over time, solutions have changed to increase comfort and convenience but have decreased in effectiveness. The development of new lens polymers raises issues of how the new polymers interact with care products, microbes, and disinfection agents. Fusarium is able to survive and replicate in drying films of care products and to adhere to and penetrate contact lenses. Additives to disinfection products can provide a safe haven for microbial growth. Rubbing improves the removal of microbes, but the labeling on care products emphasizes convenience over efficacy.

Outbreaks are the result of conditions of use and declines in efficacy. He recommended that FDA redesign testing procedures to reflect conditions of use and misuse, including topping off and microbe survival in drying films. Testing should include a variety of microbes and of lens polymers. Labeling should emphasize efficacy over convenience, starting with removal of no-rub claims. There should be a national campaign to raise awareness of good contact lens care practices.

Dr. Simon Kilvington said AMO paid for his travel and that his research has been supported variously. *Acanthamoeba*'s ability to transform into a dormant, highly resistant cyst stage is part of the reason for the microbe's ubiquity. AK is difficult to treat due to this cyst stage. Contact lens wearers make up 90 percent of recorded cases of AK, and lens care noncompliance is a major risk factor. Rates of infection are higher in the United Kingdom due to tap water contamination. There is no standard for testing efficacy testing solutions against the microbe. His laboratory found that *Acanthamoeba* trophozoites incubated in one contact lens solution formed cysts. Another solution caused mass clumping of *Acanthamoeba* trophozoites , which protects them from disinfection. His laboratory also found varying efficacy of solutions against different species strains or cysts grown under different conditions.

A laboratory screening method is to add 100 trophozoites or cysts to the solution and to culture for survivors after a fixed period of time. Cysts are typically more resistant than trophozoites. The best solution for killing both is the two step three percent hydrogen peroxide solution. Solutions were much more effective at removing *Acanthamoeba* when the rub and rinse steps were included. He recommended educating practitioners and users to include the rub step and extend disinfection time to six hours to overnight. Standardized methods must be developed, looking at physiological response to solution, biocidal efficacy, and regimen. Methods must address variations in species and strain as well as cyst production.

Dr. James Thimons said that AMO paid for his travel and that he has financial relationships with AMO, Alcon, Allergan, Inspire, ISTA, Carl Zeiss, Meditec, and Synamed. He said his concern was corneal staining. Inability to maintain a healthy ocular surface subjects the patient to risk from an immunosuppressant perspective, in the role of the contact lens on the surface of the eye, and in the use of adjunctive chemicals to maintain the health of the system. So far, there is no standard for assessing biocompatibility that can be used to assess and maintain ocular health. Scanning electron microscopy provides an assessment tool, but it is not widely available, and there is confusion in the field about corneal staining. Studies have not definitively correlated staining to risk of microbial disease. All of the relevant studies used different protocols, and lack of uniformity caused a lack of evidence-based information. He said there is no significant correlation between short-term staining and damage to the eye. The various formulations and lens materials must be evaluated individually, not by class. He suggested that FDA, industry, and clinicians collaborate to better define the materials, formulations, and risks.

Dr. John Lally, AMO's Vice President of R&D, spoke on the balance between disinfection efficacy and corneal health, the unreliability of two hour staining in predicting long-term biocompatibility, enhanced disinfection efficacy testing standards, and data supporting a rub and rinse regimen. He said formulation development and preclinical testing should incorporate real-life testing that accounts for the properties of different lenses and patient noncompliance.

MPS development strives to attain high disinfection efficacy with low cytotoxicity. Solutions with high disinfection efficacy can compromise the cornea. Two hour short-term staining does not reliably correlate with clinical biocompatibility, and the long-term relevance is controversial. Degree of staining varies depending on time of observation. IER matrix study data seems more relevant with three month wear time and represents a better long-term indicator of the real-world clinical situation. Progress is being made in *Acanthamoeba* testing, but nonstandardized methods produce variable data. Reducing infection will require implementing standardized disinfection requirements, educating the wearers, and monitoring water quality. Rubbing and rinsing is paramount. In evaluations, it is important that the microorganism adhere to simulators, since the importance of the rub step increases as microbes are given time to adhere to lenses. The simulator should be soaked in the inoculum for a reasonable period of time. He said all parties must collaborate for progress.

Dr. Mark Wilcox said his research has been sponsored by CIBA Vision and AMO. He discussed the association between solution-induced corneal staining and corneal inflammatory events. The IER matrix study was a series of trials examining the performance of lenses and solutions. The rate of solution-induced corneal staining is dependent on combinations of lenses and solutions. Hydrogen peroxide causes the least staining. Polyquad Aldox causes the most, especially with Purevision lenses. The Andrasko two hour staining grid was not found to predict three-month clinical findings. He found that the use of a MPS showed a 10 times greater risk of producing corneal inflammation. While MPS caused both corneal staining and inflammation, there may not be a causal connection between the two. Staining is not predictive of microbial keratitis.

When MPS were used with and without rubbing, the rub and rinse procedure reduced bacteria and microorganisms significantly over rinsing only. However, different lenses showed different levels of bacterial adherence. Reliance on solution-induced corneal staining as a measure of inflammation is questionable, and the clinical consequences of solution-induced corneal staining are not known. He said a rub/rinse combination is superior to no-rub in disinfecting contact lenses and should be recommended to all wearers.

Dr. David Hansen said he has worked with nearly all the companies and now works at AMO. He noted two recent studies that demonstrated efficacy of the rub and rinse technique. The Ahearn Zhang study showed that failure to use a manual cleaning procedure may help explain the increased incidence of *Fusarium* keratitis and that vigorous rinsing without the rub may cause some fungal attachments. A controlled rub/rinse regimen can remove nearly 99 percent of the microbes and attachments from contact lenses. The study demonstrated that rinsing hydrogel lenses was not significant in the disinfecting process and advocated using the rubbing step with MPS with hydrogel and possibly silicone hydrogel lenses. The literature shows that failing to rub lenses is not a prudent behavior. Many professional organizations and the literature have recommended the rub/rince regimen as part of the compliance system, along with proper hygiene, case care and replacement, and follow-up and documentation by practitioners.

AMO supports communication with all parties, especially patients. It has initiated a consumer education program that includes educational materials sent to practitioners, patient brochures, compliance contracts, educational posters, educational materials, patient reminder cards, and an acrylic practice lens. AMO leads the industry in using packaging to ensure compliance.

Dr. Francis Mah represented the American Society of Cataract and Refractive Surgery. He disclosed having received research support from Alcon and Allergan for unrelated research. He said that in 34 million contact lens wearers in the US, there are 30,000 cases of bacterial ulcerative keratitis per year. In patients with lens-related keratitis, half of patients result in best corrected vision of 20/60, a quarter result in 20/200 or worse. Bacterial keratitis results in 330 corneal transplants per year. Following the AK outbreak, the ASCRS Infectious Disease Task Force released a statement to the membership recommending that they remove and return all AMO Complete MoisturePlus Solution from offices, advise all patients of the association between the solution and infection, and advise all patients to rub their lenses with an alternative

solution, avoiding the no-rub technique. Clinicians should watch for early signs of keratitis and use dyes to differentiate the lesions from herpes-related lesions. Broad spectrum antibiotics are usually indicated. If the infection does not respond, corneal scrapings and confocal microscopy should be used to identify the pathogen. Lenses, cases, and solutions should be collected for culturing. Steroids should usually be avoided in these cases. Referral to a specialist was recommended to aid in early diagnosis.

He advocated collaboration among federal, clinical, research, and industry leaders to approve a treatment for the infections, advocate proper hygiene, recognize confocal microscopy as a diagnostic tool, and establish standards for disinfection.

Dr. William Benjamin spoke for the American Optometric Association's Commission on Opthalmic Standards. He disclosed being an expert witness in a patent case for J&J Vistakon and that nearly every company in the room had funded his laboratory. He introduced Dr. Louise Sclafani, Chair of AOA's Contact Lens and Cornea Section. **Dr. Scafani** disclosed having served on advisory panels for Alcon, Allergan, AMO, Bausch & Lomb, CIBA, Cooper and Vistakon. She asserted that solutions are going to market without adequate testing. She advocated improved labeling and strengthened pre-market testing to reflect more realistic conditions.

She said the isolates used should be expanded. Standardized testing should be developed, and products should be compared for efficacy. Products should be tested under no-rub, no-rinse conditions to account for patient noncompliance and to increase efficacy levels. Cidal activity should be tested using in vitro organic soil and a simulation of biofilm. Emerging antimicrobial coating technologies should be retested with solutions and cases for compatibility, and lens/solution combinations should be tested for lens uptake and changes in lens parameters.

As the consequences of solution-induced staining are learned, they should be incorporated into the guidance document. To aid in case-related compliance, new cases could be required to accompany every new full-sized bottle. The guidance document can also be improved by improving labeling on lens care with a statement on hand-washing, a warning to not top off solutions, rub and rinse recommendations, and a mandatory discard after opening date. She recommended mandatory post-market surveillance.

Dr. Charlotte Joslin presented for the American Academy of Optometry. She noted that, unlike in the ReNu with MoistureLoc recall, the Complete MoisturePlus recall did not effectively decrease infection rates. She said that studies show *Acanthamoeba* to be largely resistant to MPS. However, two step hydrogen peroxide solutions have proven effective against cysts. She noted that efficacy testing may not reflect the virulence of wild strains, and effectiveness is challenged by patient noncompliance. Isolates from AK patients were found to be genetically identical to the isolates from the tap water in their homes, so tap water is the likely source. She suggested that there is an increased environmental load of *Acanthamoeba*, due to EPA-mandated changes in water disinfection practices. Studies demonstrate greater *Acanthamoeba* adherence to hydrogel lenses. MPS use without rubbing is inadequate to prevent infection, and MPS are a contributing factor to the outbreaks. She recommended that all MPS be required to have a rub and rinse regimen mandated on the labeling, that solutions be tested to demonstrate

efficacy against *Acanthamoeba*, and that there be ongoing surveillance to identify infection trends and contributing factors.

Dr. Dwight Cavanagh of the University of Texas at Dallas, spoke on his own behalf. He shared recent, peer-reviewed data. The study compared daily wear patients to extended wear patients to find out if preserved solutions had an effect on pseudomonas binding to shed cells. In MPS groups, there was a consistent rise over the first three months followed by trailing to baseline, suggesting an adaption to lens wear. Dr. Stapleton's Australian paper established a greater risk of microbial keratitis infection in the first six months of lens wear. However, non-preserved solutions like hydrogen peroxide do not make the corneal surface more likely to bind with *Pseudomonas*.

In a study of 20 medical students using care solutions without lens wear, every solution, including the boric acid control, increased bacterial binding to shed cells irritated by the preservative. Since exfoliation decreases with lens wear, that increases microbial keratitis. Solutions will have to be part of the matrix of preventing infection. He suggested that, like in 1986, a task group meet, including representatives from the ISO communities. Since hydrogen peroxide is the most effective solution, he suggested that it be the gold standard that all MPS must meet. He suggested that FDA develop a white paper outlining a framework upon which to base decisions.

Sheila Kinsey spoke as a member of Prevent Blindness America about her struggle with *Acanthamoeba* infection. She asked that FDA protect contact lens wearers from solutions that provide no protection. She spoke of various members of her group and its online forum who suffer from the disease. She contracted the disease in 2001, having worn soft contact lenses for two years. She was scrupulously compliant about water contact, hygiene, and lens care. The infection, which began with swelling, and progressed to pain, photosensitivity, and oozing, baffled her doctors and caused her to take a leave of absence from work. She went to USC Doheny Eye Center and received a biopsy in 2002, confirming *Acanthamoeba* infection. She moved to Iowa to get care. She has had seven corneal transplants and dozens of other procedures. Off-label use of high doses of IV pentamidine preserved her eye structure but caused bleeding stomach ulcers requiring emergency transfusions. She no longer has signs of active *Acanthamoeba* but required further eye surgery after her hospitalization.

FDA AND CDC PRESENTATION

Dr. James Saviola introduced the presentations. FDA has reassessed the current guidance for MPS and sees new concerns with new lens materials and product formulations. The post-market experience is being redirected into pre-market review. FDA is involved in laboratory studies, standards development, and discussions with manufacturers. FDA sought Panel input to aid in this transition.

Dr. Gene Hilmantel presented on the *Fusarium* keratitis outbreak. Before the outbreak, fungal keratitis had been rare. In February of 2006, there were reports of a significant number of cases of Fusarium keratitis in Hong Kong and Singapore. The Singapore cases were linked to Bausch & Lomb contact lens solutions. In March 2006, CDC began

receiving reports of US cases, prompting a CDC and FDA investigation. CDC conducted a case control study, collecting cases actively and passively. Neighborhood matched adult wearers were the control, and confirmed cases were those with positive corneal cultures. Confirmed patients, control patients, and treating physicians were interviewed. Passive surveillance identified 180 confirmed cases between June 2005 and September 2006. Analysis found two risk factors. Use of Bausch & Lomb ReNu MoistureLoc solution has an odds ratio of 13.3, and reuse of the solutions in the case (topping off) had an odds ratio of 3.2.

Fusarium was not found in any unopened product, and the cultured strains showed genetic diversity. No evidence of contamination was found at the manufacturing facility, retained lots, or the facility's water. However, the number of cases corresponded with Bausch & Lomb MoistureLoc's market share over time. After discussions with FDA, Bausch & Lomb ceased sale of the product and initiated a recall. The number of cases dropped rapidly after the recall, and the outbreak ended within two months.

FDA and Basch & Lomb looked into why the outbreak had occurred. MoistureLoc has two ingredients not found in other multipurpose solutions: alexadine, a disinfectant; and polyquarterium 10, a moisture-retaining polysaccharide. It also had a high content of poloxamer

407, a surfactant. Premarket testing had shown high efficacy against fusarium.

Dr. Jennifer Rabke Verani from CDC, discussed the *Acanthamoeba* keratitis outbreak. AK is a rare and potentially blinding infection of the cornea by an environmentally ubiquitous free-living amoeba. Known risk factors were poor contact lens hygiene and contact with non-sterile water while using lenses. The estimated annual incidence rate is one or two cases per million contact lens users. In May 2006, the Illinois Department of Public Health notified CDC of a possible increase in AK cases in the Chicago area. CDC contacted ophthalmologists in other areas, and it was unclear whether or not cases were increasing. In January 2007, CDC surveyed 22 ophthalmology centers nationwide for historical AK case numbers. The survey indicated that cases had dramatically increased in the past three years. This prompted a multi-state outbreak investigation, starting in March of 2007. The objectives were to quantify and characterize the increase in AK cases, identify risk behaviors, and recommend prevention measures.

Cases, people diagnosed 2005 or later with a positive corneal culture, were found through Epi-X, optometry and ophthalmology associations, and queries of microbiology labs and ophthalmology centers. Case patients, treating ophthalmologists, and the patients' eye care providers were interviewed. In May, a preliminary analysis found a significant association with use of AMO's Complete MoisturePlus multipurpose solution. AMO voluntarily recalled the product.

In the preliminary analysis, the controls from the Fusarium study were used. After the recall, a matched case control study was done. Controls were matched by contact lens use (soft lenses, hard lenses, or no use), and geographic location. Standardized phone interviews were used. 105 case patients were interviewed and included. Patients were widely distributed geographically. 89 percent of the patients were contact lens users, and 88 percent of those wore soft lenses. Most common presenting symptoms were pain, redness, sensitivity to light, and a foreign body sensation. The median time from symptom onset to AK treatment initiation was 49 days.

In the 85 patients with clinical outcomes available, 28 percent had corneal transplant performed or planned. In the 70 percent with current vision data, 41 percent had visual acuity of 20/200 or worse with corrected vision in the affected eye.

On univariate analysis, case patients were more likely to be male, under age 25, and Hispanic. Ocular trauma was uncommon in both groups but more common among cases. Cases were more likely to have used contact lenses for five years or fewer. Swimming in a lake or river with contact lenses in was a significant risk factor, but washing the face with contact lenses was protective. The use of AMO Complete MoisturePlus was a major risk factor. Ever topping-off solution was also an important risk factor. Always capping the solution bottle after using it was associated with disease. Cleaning lenses at the bathroom sink, compared to in the bathroom but not at the sink, and always washing hands before inserting lenses were both protective. Less frequent replacement of old contact lens with new ones also appeared to be protective.

On multivariate analysis, only three variables remained statistically significant. After adjusting for age and gender, case patients were 16.8 times more likely than controls to have used AMO Complete MoisturePlus. They were 2.8 times more likely to report ever topping off solution and 2.8 times more likely to have used contact lenses for less than five years. No association was found between AK and any other contact lens solution type or product. Contact lens characteristics, aspects of contact lens use, contact lens hygiene and disinfection practices, and water exposure variables were not significantly associated with risk of AK. Many of those variables have been hypothesized or found to be risk factors in other studies.

AMO Complete MoisturePlus was launched in 2003, just before the nationwide increase in AK cases. No evidence of contamination was found, and lot numbers used by patents did not show repetition. CDC suspects insufficient anti-*Acanthamoeba* activity to be the cause of the outbreak. A concurrent study in Chicago also found AMO Complete MoisturePlus to be a primary risk factor.

The AK and Fusarium keratitis outbreaks occurred concurrently among soft contact lens users. In both outbreaks, a particular MPS was the primary risk factor, though there was no contamination. In both outbreaks, topping off was also an important risk factor. When ReNu with MoistureLoc was tested under circumstances simulating topping off, reduced antimicrobial efficacy was found. The two outbreaks have raised concerns about the safety of MPS.

Ophthalmology centers and microbiology laboratories were recontacted for 2007 data. There is neither a clear rise nor fall in AK in the seven months fallowing the recall. This may be due to diagnostic delay or continued use of the product. There are reports of patients continuing to use the product. Limitations of the investigation include patients' limited recollection of the products they'd used, reporting bias due to the recall, inability to assess the role of water treatments, and the small number of non-contact lens users and rigid contact lens users. Follow-up is being completed, and a survey is planned for the first half of 2008 to assess the impact of the recall.

Dr. Bernard P. Lepri spoke on what is known about contact lens wearers. There are over 30 million contact lens wearers in the United States; 67.7 percent of them are female; they are predominantly myopic; and half of them are 25 to 44 years old. Eighty percent of them wear daily wear soft lenses and 15 percent wear extended wear soft

contact lenses. More than 50 percent wear one-to-two-week disposables. Care regimens for lenses have grown more complicated with time, and 80 percent of contact lens complications are related to noncompliance with wear and maintenance. The wearer's perception of his or her compliance behavior is essential to minimizing complications. This has been demonstrated in several studies. Noncompliance among contact lens wearers is higher than in the general medical population.

Factors affecting compliance include the complexity, frequency, duration, and cost of the regimen. Noncompliance is highest in conditions that are asymptomatic, prophylactic, or suppressive in nature. Studies show high noncompliance rates and that reinforcement during follow-up improved behavior.

Human factors are important for contact lens safety. The goal of human factors engineering is to make products safe, efficient, and easy to learn and use by understanding how the consumer uses the product in the real world. What was once called user error is now called use error to spread the blame for misuse to include design and labeling. From this point of view, the manufacturer has the responsibility to reduce use error through proper design, testing, and labeling. Human factors engineering is especially challenging for contact lenses and care products. Common use errors with contact lenses include irregular cleaning of lenses, poor hand hygiene, using tap water or saliva to wet lenses, not following replacement schedules, lack of regular eye exams, and irregular replacement of disinfecting solutions.

He recommended that labeling provide written instructions as well as reasons for the various procedural steps and the consequences of not following them; that eye care professionals reinforce lens care regimens with their patients, using patient and practitioner guides; that care products be designed and tested consistent with consumer use patterns; and that product labeling include a discard date for use after opening the product.

Carol Clayton of the FDA spoke on patient labeling. Labeling statements are developed using principles from the 2001 guidance document on patient labeling, which gives four elements of an effective warning: a signal word, a hazard avoidance directive, a clear statement on the nature of the hazard, and a description of consequences. Based on those principles, new proposed patient labeling has been developed, based on recommendations in the 2006 and 2007 Advice to Patients With Soft Contact Lenses documents. The proposed recommendations include a warning against reuse and topping off, instructions to rub and rinse lenses, instructions on proper lens case care, and a warning to remove lenses before any water activity.

Dr. Joseph C. Hutter presented on lens and solution compatibility issues. FDA regulatory groupings for contact lens material were developed to categorize lens behavior when used with different care product solutions and with proteins in the tear film. Three types of monomers are used in conventional contact lenses: hydrophilic monomers, hydrophobic monomers, and crosslinkers. For hydrogel lenses, the main hydrophilic monomers are HEMA (hydroxyethyl methacrylate), GMA (glycerol methacrylate), VP (vinyl pyrrolidone) and MA (methacrylic acid). Currently, lenses are grouped into four categories: Group 1, non-ionic hydrogels less than 50 percent water; Group 2, non-ionic hydrogels greater than 50 percent water; Group 3, ionic hydrogels less than 50 percent

water; and Group 4, ionic hydrogels greater than 50 percent water. These groupings affect how devices are tested.

The grouping works well for conventional materials, but the limitations of the grouping became apparent when silicone hydrogels entered the market. There were two well-known solution incompatibilities with silicone hydrogel lenses: AMO UltraCare Disinfecting System with Bauch and Lomb PureVision and Ciba SoloCare with Vistakon Acuvue Advance. In both cases, the products distorted the lenses. Precautions were put on the labeling. SoloCare was replaced and is no longer on the market. The causes of the incompatability were never determined.

As lenses have changed, formulations of care products have become more complex. Solutions have been developed to clean and disinfect in one step and new components have been added for comfort, moisture retention, conditioning, and lubrication. In ReNu MoistureLoc, a polymer added to retain moisture on the lens is thought to have interfered with *Fusarium* disinfection under certain conditions. In AMO Complete MoisturePlus, propylene glycol was added for moisture retention, and it may have contributed to the *Acanthamoeba* outbreak. ISO is considering adding a fifth group for silicone hydrogels under ISO 18369-1. Dr. Hutter proposed subdividing the group based on pore size, ionic content, surface properties, and silicone phase considerations. Silicone hydrogel technology is currently represented by four types of lens: lotrafilcon B, balafilcon A, galyfilcon A, and comfilcon A. More are to come, and an effective grouping system is needed. He recommended having silicone hydrogel lenses as a separate group and stratifying that group into subcategories.

Ms. Myra Smith discussed microbiology issues. FDA recognizes the ISO 14729 stand alone and regimen tests for disinfection efficacy and ISO 14730 for antimicrobial preservative efficacy for solutions packed in multi-dose containers. The ATCC bacterial strains used in the stand alone and regimen tests are *Pseudomonas aeruginosa, Staphylococcus aureus, Serratia marcescens, Candida albicans,* and *Fusarium solani.* The stand alone test measures the rate and extent of microbial kill under ideal conditions: the potency of fresh solution directly from a sealed container, with no lenses added to the solution. FDA recommends this testing scheme for products with digital rub and rinse directions. When ISO 14729 was written, cleaning instructions had separate rub and rinse steps.

To address concerns raised by no-rub products, FDA recommends that organic soil be added to the stand alone test and the entire care regimen's ability to kill and remove organisms be tested. The current test simulates use under the proposed directions for cleaning and disinfecting lenses. The test measures physical removal of high inoculum and microbial kill of remaining inoculum during the rub and rinse steps. Silicone hydrogel lenses are not included in this testing.

The antimicrobial preservative efficacy test evaluates the system's ability to prevent contamination in the product for 30 days. Testing includes a re-challenge at day 14. The effects of preservative uptake by the lenses are not tested. The test organisms are *Pseudomonas aeruginosa, Staphyloccus aureus, Escherichia coli, Candida albicans* and *Aspergillus niger.*

As evidenced by the outbreaks, the tests should be improved. Updating is also needed due to changes in lens materials, care product formulations, and directions for use. Tests should better predict real world performance.

An FDA and CDC study found that alexidine uptake by lenses during soaking reduced the preservative concentration in the lens case, decreasing antimicrobial efficacy against *Fusarium* solani. ANSI and ISO are developing a method to evaluate disinfection efficacy in the presence of a lens and case. The methods will include measurement of preservative at various intervals, use a variety of lens types, and measure log reduction of ISO 14729 challenge organisms. FDA will help validate the methodology.

Other issues are that microbial attachment may vary by lens type, organism species, and organism strain; biofilm may be strongly attached to lenses or resistant to care product preservatives; and current testing methods do not evaluate the effect of biofilm on disinfection efficacy.

FDA is reconsidering the advisability of the no-rub regimens, since rubbing can remove microorganisms, debris, and deposits from the lens prior to disinfection. FDA asked for Panel recommendations on the need to include rub and rinse directions, revising the regimen test to better predict real-world performance, adding *Acanthamoeba* as a challenge organism to the disinfection efficacy tests, developing tests on the effects of preservative uptake by contact lenses on disinfection efficacy as a basis for recommended storage time and to identify lens/solution incompatibilities, and the proposal to conduct microbiology effectiveness using worst case conditions, such as testing at the low end of active ingredient specification or with resistant clinical isolates.

Dr. G.S. Visvesvara of the CDC spoke on resistance of *Acanthamoeba* cysts to disinfection in various contact lens solutions. *Acanthamoeba* is a hardy organism with a two-stage life cycle: trophozoite and cyst. In addition to AK, *Acanthamoeba* can cause amebic encephalitis, sinus infections, and lung infections. There are over 20 species of *Acanthamoeba*.

In response to the outbreaks, he took 11 contact solutions from area stores and tested them against *Acanthamoeba* cysts of different species: A.castellanii, A. polyphaga, and A. hatchetti. He used freshly isolated, not axenic, strains. Ten microliters, containing 100 cysts, was put in one ml of contact lens solution and incubated for four or six (according to manufacturer's instructions) and 24 hours. The organisms were then washed in contact lens solution and cultured on agar plates coated with *E. coli*. Many of the cysts excysted in two to three hours, even after 24 hours of exposure, and with most solutions, the plates were fully colonized. Only Ciba Vision Clear Care, which uses hydrogen peroxide, inactivation of the cysts in all three species of *Acanthamoeba*. Only Ciba Vision Clear Care and B&L Boston Simplus showed any activity against *A. castellanii* cysts. Solutions without hydrogen peroxide had varying activity against *Acanthamoeba*, but none had any activity at four hours of contact time. Some had activity after 24 hours, but most contact lens wearers do not soak their lenses for 24 hours.

Dr. Molly Ghosh presented on lens/solution interactions and impact on biocompatibility. The 1997 guidance document is currently followed for testing care products. Silicone hydrogel lenses were introduced in 1999, and use has been increasing. Current

toxicological test methods do not evaluate the effects of interactions between lenses and care solutions.

The *Fusarium* keratitis outbreak's cause is unknown, but could be multifactorial, including patient behavior, cytotoxic effects of the solution on the epithelial barrier, or loss of antimicrobial activity during lens storage. In development of MPS, antimicrobial efficacy must be balanced with avoiding cytotoxic effects on contact with the eye directly or via the lenses. Lenses can take up chemical ingredients during soaking and release the chemicals during wear that can cause corneal toxicity. A compromised corneal surface is at increased risk of infection.

In response to the *Fusarium* keratitis outbreaks, ISO formed a working group to explore alternative preclinical test methods for potential lens/solution interactions. FDA prepared a draft proposal on cytotoxicity testing of MPS to include potential toxic effects of the solution and cytotoxic effects arising from lens/solution interaction. It was discussed at the March ANSI meeting and will be discussed at the July ISO meeting. While the 1997 guidance recommends toxicity testing of the solution alone, the proposal includes testing the solution alone and in combination with various lenses: Group 1 and Group 4 hydrogels and representative silicone hydrogel lenses with different surface treatments. Silicone hydrogel lenses should be included in testing regardless of whether or not the MPS is indicated for use with them, since solutions are over the counter products. FDA believes that both in vivo and in vitro tests are needed to evaluate MPS. The rabbit model is recommended for in vitro testing, L-929 mouse cell culture model for cytotoxicity testing.

For cytotoxicity testing, FDA proposed the ISO/USP test methods with the L-929 cell model. Tests are designed to evaluate potential cytotoxic effects due to direct exposure to the MPS and indirect exposure through contact lenses. Both conventional hydrogel and silicone hydrogel lenses will be tested in this assay. In addition to the currently-used agar diffusion assay, a modified elution assay will test the solution with a cell culture media. Additionally, there is a proposed test of MPS-soaked lenses for cytotoxicity: a direct contact assay in which the lens touches the cells.

Dr. Marc Robboy of FDA presented on the impact of silicone hydrogel contact lenses on clinical study methodology. Current 510(k) guidance recommends that new care products be tested clinically using a matrix of 60 lenses from Groups 1 and 4. However, silicone hydrogel lenses do not interact with the eye or with care products the same way conventional hydrogels do. There have been reports of solution-related complications with silicone hydrogel lenses, including generalized mild punctate corneal epithelial staining. This is attributed to the lens care preservative being taken up by the lens and subsequently released onto the eye.

Corneal staining occurs at different rates with different combinations of lenses and solutions. There is disagreement as to its effects. Some researchers recommend that follow-up occur at the time of maximum staining severity, which is two to four hours after lens insertion. Current FDA guidance recommends follow-up but does not specify the time of day. He requested Panel guidance on the recommendation that there be follow-up at two hours after insertion to assess for corneal staining.

Until silicone hydrogel lenses are properly grouped, he proposed an interim approach that subdivides silicone hydrogel lenses by surface treatment. In lenses with

similar chemistry, the lens with the higher water content should be tested. The four groups: lotrafilcon B, balafilcon A, galyfilcon A, and Group 4, would require a total of 180 lenses for testing. The approach will evolve as new lenses are approved.

FDA has cleared both rub and rinse as well as no-rub MPS. However, in response to the outbreaks, various professional organizations recommend the rub and rinse method. He requested Panel input on whether or not to continue having no-rub directions on product labeling.

PANEL DISCUSSION AND QUESTIONS

1) **Please discuss whether our proposed directions for use and warnings below are warranted. If yes, please identify any other message(s) that should be conveyed in the proposed warnings:**
   - **A. Reuse and topping off;**
   - **B. Rub and rinsing time;**
   - **C. Lens case care;**
   - **D. Water activities;**
   - **E. Specifying a lens care product discard date.**

   Please provide any additional recommendations for product labeling.

Panel consensus was to warn strongly in clear language against reuse and topping off. Since rub and rinse maximizes solution efficacy, a realistic minimum rub and rinse time should be in the labeling, along with an explanation of why to rub and rinse. It should be made clear that rinsing is in solution, not water. For lens case care, the Panel favored FDA's proposed warning, with added clarification on avoiding water. The Panel said there is insufficient information to comment on how often a case should be replaced or how it should be dried. There was a suggestion to strengthen the warning to include the risk of vision loss, and consider if the risk should include the term "blindness". On the warning against wearing lenses during water activities, the Panel noted that the warning was not consistent with extended wear guidelines. The warning creates confusion. Patients prefer to wear lenses when being active and may need to wear lenses, since reduced vision may create a risk of injury greater than the risk of AK. The warning might recommend removing the lenses after water activity. There was general consensus of there being a risk of eye infection from water and a suggestion that the labeling should refer the patients to their eyecare providers. Disposable single-use lenses have an advantage in a contaminated environment. Fundamentally, the Panel supported a warning on water exposure but had difficulty finding consensus on what to recommend. On specifying a lens care product discard date, there was discussion of limiting the size of bottles and including a discard date to encourage compliance. The Panel recommended that there be a date of discard after opening and recommended that it be done in such a manner as to encourage compliance. Additional recommendations from the Panel were to make the warnings very visible on the website.

2) **Currently rub and no-rub care products have been cleared by the FDA for marketing in the United States. In light of all the data currently available,**

please discuss your recommendations for continuing to have no-rub directions in the product labeling.

Panel consensus was to say that there is a certain level of improvement obtained with rub and rinse compared to rinse alone and that no-rub solutions should be allowed, provided they meet the standard of efficacy met by rub and rinse. In the short term, rub and rinse should be encouraged and no-rub discouraged until new methods are standardized and applied to all products . In the long term, benchmarks should be established so that products can meet the efficacy level of rub and rinse.

3) **Regarding Clinical Issues**
   - **A. Please discuss your recommendations for an additional follow-up visit at 2 hours in order to assess for solution-related corneal staining.**
   - **B. Please discuss whether this additional should be included in lens care products and/or lens guidance.**
   - **C. Please provide your recommendations on the inclusion of silicone hydrogel lenses in the clinical investigations of contact lens care products.**

Because there was no demonstrated correlation between corneal staining and keratitis, it was unclear how the follow-up data would help, and compliance would be burdensome, the Panel did not recommend the addition of follow-up for corneal staining. The Panel said silicone hydrogel lenses should be included in clinical investigations and expressed approval of FDA's proposed subdivisions, with room for further evolution as other classes develop. Sponsors could negotiate for fewer classes when appropriate.

4) **Regarding Microbiology Issues**
   - **A. Please discuss your proposal to revise the current Regimen Test in order to improve predictability of "Real World" performance and include the following topics in your discussion:**
     - *** Testing marketed silicone hydrogels**
     - *** Defining 'worst case' rub and rinse times (e.g. 5 sec. rub and 5 sec. total rinse time)**
   - **B. Please discuss your recommendations for adding *Acanthamoeba* as a challenge organism in disinfection efficacy testing.**
   - **C. Please discuss our proposal for developing standardized test methods to evaluate the effects of preservative uptake by contact lenses on disinfection efficacy. Additionally, please comment on use of these tests to determine post-disinfection storage times in an unopened lens case.**
   - **D. Please discuss our proposal for modifying Disinfection and Preservative Efficacy testing by:**
     - *** Testing at the lower end of the active ingredient specifications to simulate worst case conditions.**
     - *** Including more resistant clinical isolates in these tests.**

For part A, Panel consensus was to do real-world testing with a lens in the case with the solution, no-rub, no-rinse and with biofilm. For part B, the Panel supported *Acanthamoeba*'s inclusion as a challenge organism, using a relevant strain such as environmental organisms and isolates from infected patients when possible. There was discussion of testing methods other than culturing, such as PCR and confocal microscopy. The most virulent organisms should be used, in troph and cyst form. The test must be standardized, and the log reduction units must be meaningful. Under C, the Panel discussed the proposals from Ms.. Smith's presentation. The test method should include the lens. If the gold standard is not sterility, there should be a limit on how long the lens can sit in the solution, and it should be short. Panel consensus was to agree with FDA's proposals on developing guidelines. For Part D, the Panel generally agreed with testing at the lower end of the active ingredient specifications. Like testing high concentrations for toxicity, testing low concentrations for efficacy using resistant isolates is a way of testing the worst case. When hydrogen peroxide solutions are tested, there should be a way to standardize the neutralization effect and account for differences between peroxide-based solutions and multipurpose solutions.

5. **Please discuss whether you agree with:**
   - **ISO's current consideration of having silicone hydrogel lenses as a separate group and;**
   - **FDA's plan to further stratify the silicone hydrogel lens group into subcategories.**

Panel consensus was that it does make sense to stratify the groups.

6. **The current cytotoxicity test involves testing on the multipurpose solution by itself and not in conjunction with various groups of lenses. Please discuss our proposal to include both conventional and silicone hydrogel contact lens soaked in a multipurpose solution for Direct Contact cytotoxicity testing to evaluate the multipurpose solution.**

The Panel was in favor of both incorporating conventional and silicone hydrogel lenses into the testing.

ADJOURNMENT

The day's agenda completed, Chairman Bressler thanked the participants and adjourned the meeting at 4:10 p.m.

I certify that I attended this meeting of the Ophthalmic Devices Advisory Panel on June 10, 2008, and that these minutes accurately reflect what transpired.

Karen F. Warburton, M.H.S.
Executive Secretary

I approve the minutes of the June 10, 2008 meeting as recorded in this summary.

Neil M. Bressler, M.D.
Chairperson (Acting)

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