CATARACT

FDA Update: Next-Generation IOLs

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INTERVIEWING DAVID F. CHANG, MD, MALVINA B. EYDELMAN, MD, DOUGLAS D. KOCH, MD, WILLIAM H. MAISEL, MD, PHD, AND THOMAS A. OETTING, MD

While hundreds of monofocal intraocular lenses (IOLs) are on the U.S. market, only 10 of the so-called "premium IOLs" are available. Why is it taking so long to get more of these lenses approved? And are there ways to expedite the process? The Academy and the U.S. Food and Drug Administration (FDA) explored these questions and more in a first-ever collaborative workshop held this spring.[1]

More than 230 clinicians, researchers, FDA leaders, and industry representatives met to discuss novel endpoints for premium IOLs, covering such topics as adverse events (AEs), methods for assessing visual disturbances, and surgeons' expectations for IOLs providing near vision. In addition, they discussed a new type of IOL known as the extended depth of focus IOL (see "New Kid on the Block").

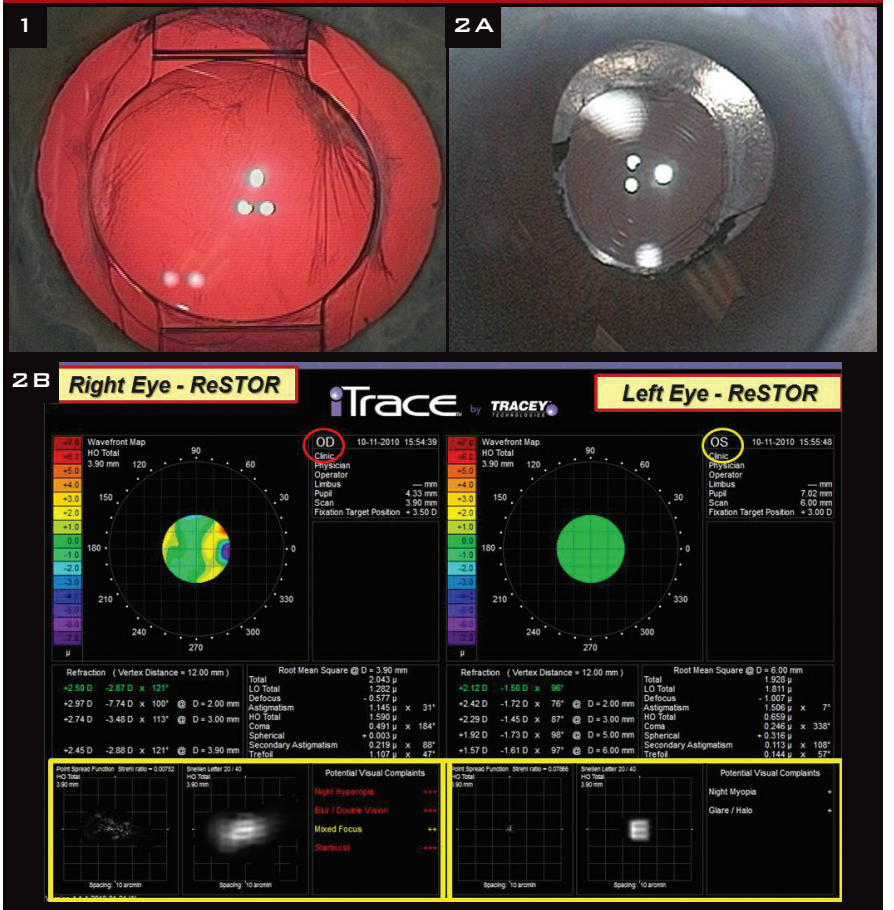
Here's an overview of the daylong proceedings, including highlights from the individual breakout sessions.[2]

The Road to Approval

Today, approximately 14 percent of cataract patients receive one of three types of premium IOLs: accommodating, multifocal, or toric; a fourth type of premium IOL is the phakic IOL. (Although there is considerable controversy in the ophthalmic community about the term *premium*, this article uses the nomenclature from the workshop.) The FDA has received an increasing number of requests for review of additional entries, but the process for review is a cumbersome one.

"Currently we have a limited availability of FDA guidance or recognized standards. As a result, we evaluate many submissions on a case-by-case basis," said Malvina B. Eydelman, MD, at the FDA. "Both the FDA and sponsors spend significant resources on repeat submissions, and there's a delayed or limited benefit to other devices with similar characteristics."

Potential Concerns



(1) This image shows Z syndrome associated with an accommodating IOL. (2A) IOL exchange was required for this multifocal IOL in the right eye. (2B) Ocular wavefront for both eyes preoperatively.

DAVID F. CHANG, MD

Existing roadblocks. Obstacles to approval include "a lack of consensus in some preclinical issues, on best clinical trial design, and [on] appropriate safety and effectiveness endpoints," Dr. Eydelman said. Additionally, there is a need for new categories of IOLs, "based on new optical properties and/or benefits to patients," she said.

Which way forward? "We can continue to evaluate each submission one at a time and take a long and winding road, or we can do what we're trying to attempt [in this workshop]—develop the novel endpoints for premium IOLs," Dr. Eydelman said.

Four Hot Topics

Clinicians and patients want a broader array of IOL options. Patients want to see as well as possible, and most want to minimize their dependence on spectacles. Physicians want safe products and happy patients. What measures might be used to guide IOL regulatory approvals and clinical decision making to best achieve those goals?

The workshop was organized around the following hot topics.

Safety issues. Premium IOLs have unique safety risks, "which are an inevitable trade-off for the added benefits that they provide," said Douglas D. Koch, MD, at Baylor College of Medicine. "For example, with toric IOLs, there is the occasional occurrence of postoperative astigmatism due to problems with misalignment and postoperative IOL rotation; in rare instances, this requires surgical reintervention to adjust the axis alignment."

With multifocals, he noted, "Explants may be occasionally required due to complaints about loss of contrast sensitivity and development of visual disturbances."

Because accommodating lenses must move and flex to function, Dr. Koch said that they "can present mechanical issues like Z syndrome and anterior or posterior dislocations. Patients can rarely experience glare and halos from a smaller optic zone and irregular astigmatism related to optic flexure." As for phakic IOLs, he said, "There have been reports of increased risk of corneal decompensation, uveitis, and glaucoma."

When FDA reviewers evaluate the safety and performance of a new IOL, they compare the number of patients with a particular AE to an allowed rate of cumulative and persistent AEs on what's known as the FDA "grid" (its formal name is "Safety and Performance Endpoints"). But is the current FDA grid applicable to premium IOLs?

Breakout consensus. Participants felt that the current grid needs little alteration. They recommended better definitions of some AEs; suggested minor changes to address specific lenses (such as rotation for toric lenses and endothelial cell loss for phakic IOLs); and advised that patient-reported outcomes (PROs) such as halos, glare, and negative dysphotopsias be added.

Patient-reported outcomes. A PRO refers to any report on the status of a patient's health that comes directly from the patient without interpretation by a clinician or anyone else. In outcomes studies, PROs are often used to measure the effect of an intervention on such factors as symptom impact, disability, treatment tolerability, treatment satisfaction, and health-related quality of life.

PROs are "really among the most important factors we should be considering," said William H. Maisel, MD, MPH, at the FDA. "It is no coincidence that we're focusing here on PROs because of the large subjective component to these devices." If ophthalmologists focus only on functions such as visual acuity and contrast sensitivity, they may overlook patients' thoughts, beliefs, and attitudes about their vision, several speakers pointed out.

During the workshop, participants discussed a number of issues to consider beyond the traditional statistical measures of precision, reproducibility, validity, and responsiveness. For instance, how best can the words patients use to describe visual phenomena (such as starbursts, comets, and halos) be parsed? Should a single PRO measure that encompasses all types of IOLs be developed? Finally, can a collaborative mechanism be built that would allow stakeholders to share the development costs of a PRO instrument?

Breakout consensus. Participants agreed that the concepts of subjective quality of vision and visual function are both important—and that they exist independently of a specific IOL technology. In addition, they agreed

New Kid on the Block

What do patients want? "More options!" said David F. Chang, MD, at the University of California, San Francisco. "You really can't talk about surgeon expectations for premium IOL performance without talking about patient expectations." He added, "If we had more options, we could do a much better job of individualizing the choices we give to our patients."

He and other speakers were particularly pleased with the advent of an emerging technology, the extended depth of focus IOL or EDOF IOL, which was discussed at the workshop. "Because this should improve uncorrected intermediate distance without the optical trade-offs of a diffractive multifocal, this is a technology that would appeal to many cataract patients," Dr. Chang said.

The goal of the EDOF IOL is to provide improved near and intermediate visual performance without compromising distance vision. "This could be accomplished, for example, by positive spherical aberrations of a monofocal optic," Dr. Chang said. Theoretically, patients with the EDOF IOL should be less troubled by glare and halos and experience less loss of contrast at distance, compared with a diffractive multifocal lens. However, both preclinical and clinical testing will be needed to verify this.

The advent of EDOF technology also opens the door to various combinations with other types of lenses, speakers pointed out. For instance, EDOF optics could be added to toric optics to provide extended depth of focus for toric IOLs—or added to accommodative optics to boost near performance.

that a collaborative model for PRO development should be pursued.

Objective assessment of accommodation. Accommodating IOLs, which vary the focal power of the eye, have the potential to provide an extended range of vision without loss of contrast sensitivity. Although it is possible to measure accommodation objectively in a clinical study, doing so involves addressing a number of challenges, including the advantages and disadvantages of the instruments used.

Speakers discussed ANSI/ISO draft standards for objective assessments (such as dynamic aberrometry and dynamic autorefraction) of accommodating IOLs and questioned whether the field should be developing standard operating procedures for optical and biometric methods. (For instance, ANSI and ISO require 1 D of objectively measured accommodation for a device to be called an accommodative IOL.)

Breakout consensus. Participants arrived at a clear consensus that the range of premium IOL technologies was too great to justify development of standard operating procedures for objective assessments.

Subjective assessment of accommodation. A number of variables come into play during assessment of accommodation, from lighting conditions to the nuances inherent in the interaction between the examiner and the patient. Moreover, consensus is lacking on a number of issues, such as time for testing and whether testing should be binocular or monocular (or both).

Subjective and objective tests need to be correlated, speakers said—and the results need to be further correlated with any PRO questionnaires.

Breakout consensus. Participants presented myriad recommendations, including the need to establish a subjective methodology of testing with an emphasis on defocus curves. In addition, they recommended using adaptive optics to test eye models under varied conditions.

Cautions and Conclusions

Patients with such conditions as age-related macular degeneration, epiretinal membrane, keratopathy, optic neuropathy, or prisms in their spectacles might not benefit from certain premium lenses or might experience unwanted visual effects, speakers cautioned. And patient expectations must always be kept in mind: Many who had hoped to be rid of spectacles may find themselves needing some postoperative correction, speakers noted.

Overall, the workshop was "a game changer," said Dr. Eydelman. And Thomas A. Oetting, MD, at the University of Iowa, agreed. "The FDA clearly wanted input from industry and surgeons. I felt that the meeting was indeed a 'working' workshop and that progress was made on developing assessments like PROs for premium IOLs."

Next, the FDA and the Academy will work to determine a strategy for dealing with recommendations presented during the meeting, in conjunction with the National Eye Institute. ■

1 FDA/AAO Workshop on Developing Novel Endpoints for Premium IOLs, held March 28, 2014 in Silver Spring, Md.

2 For a full transcript of the session, see www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm365646.htm.

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