The Glaucoma Research Community and FDA Look to the Future: A Report from the NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium*

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On March 13–14, 2008, the National Eye Institute (NEI), of the National Institutes of Health (NIH), and the Food and Drug Administration Center for Drug Evaluation and Research (FDA CDER) held the NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium to discuss the possible use of new structural and functional endpoints for evaluating glaucoma therapies in clinical trials. It was an important meeting where the FDA and the glaucoma research community advanced their common understanding of glaucoma clinical trials. An appreciation was gained by researchers and others within the glaucoma community of the receptivity of the FDA to new endpoints.

Glaucoma is a complex, progressive optic neuropathy. It is the leading cause of irreversible and preventable blindness, affecting an estimated 2.2 million people in the United States and 70 million worldwide. Basic and clinical research initiatives are revealing the pathobiology and clinical course of glaucoma and are setting the stage for possible new treatments.

Currently, clinical drug trials are focused on intraocular pressure (IOP) measurements and/or visual field tests (a functional outcome measure) for the assessment of clinical IOP-lowering efficacy and changes in optic nerve function. In some studies, stereoscopic optic disc photography (a structural outcome measure) has been used as a secondary endpoint. The FDA considers optic nerve and retinal nerve fiber layer (RNFL) structural changes and new changes in functional tests to be outcome measures in clinical trials that serve as the basis for approving neuroprotective glaucoma therapies, provided those outcomes are proven predictive of function that is clinically relevant to a patient.

Although there are data suggesting the early involvement of central vision, glaucoma generally affects peripheral vision first in standard clinical testing. Functional visual field tests evaluate the presence and amount of visual field loss. Clinical observation of the optic nerve and examination of optic nerve photographs can be used to determine the presence of structural changes such as narrowing of the neuroretinal rim, loss of parapapillary fibers from the RNFL, increased excavation of the optic cup, β-zone parapapillary atrophy, and optic disc hemorrhage. Accurate interpretation of the structural events has traditionally been dependent on the experience and subjective judgment of the observer.

New computerized imaging devices for viewing the optic nerve are used widely to detect glaucomatous changes in the optic disc and RNFL and also to quantitate these changes. Measurements generally are objective and reproducible. Among these imaging technologies are confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography.

The purpose of the NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium was to provide a forum for discussing outcome measures—based on the newer technologies—for evaluating neuroprotective products (i.e., those that protect the optic nerve) for glaucoma in clinical trials to facilitate bringing safe and efficacious glaucoma pharmacotherapies to the U.S. market.

The meeting was held in the Natcher Auditorium on the NIH campus. Participants from the glaucoma community left with a clearer understanding of FDA expectations for demonstrating the safety and efficacy of new pharmacotherapies, the relevancy of new endpoints, and the role of the FDA in providing guidance for meeting recognized standards for approval of new therapeutic agents.

Symposium organizers were Robert N. Weinreb, MD, University of California, San Diego; Paul L. Kaufman, MD, University of Wisconsin, Madison; Frederick L. Ferris, III, MD, NEI, Wiley Chambers, MD, FDA CDER; and Malvina Eydelman, MD, FDA Center for Devices and Radiologic Health (FDA CDRH). The meeting was managed by The Association for Research in Vision and Ophthalmology (ARVO). Most of the attendees were researchers, clinicians, policymakers, and industry and vision association representatives. The role of the NEI was extensive, including support related to meeting logistics, travel, and programming.

The meeting contained six sessions, each with presenters and discussants who were tasked by the organizers to address specific aspects of their given topics.

Meeting organizers welcomed the attendees to this first-of-a-kind event. Dr. Eydelman briefly summarized the regulatory pathways for glaucoma devices, delineating inherent differences in the regulatory pathways for glaucoma drugs and their

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implications. She emphasized the need for future workshops dedicated to development of endpoints applicable to all glaucoma devices and drugs.

**SESSIONS**

**Session 1. Optic Disc and RNFL Parameters as Outcome Measures**

**Participants.** David Greenfield, Jeffrey Liebmann, Linda Zangwill, Christopher Girkin, and Wiley Chambers.

**Discussants.** Douglas R. Anderson, Murray Fingeret, Felipe Medeiros, Joel Schuman, and Michael Sinais.

**Session 2. Visual Function Parameters as Outcome Measures**

**Participants.** George (Jack) Cioffi, Joseph Caprioli, Chris Johnson, Michael Patella, and Mark Nevitt.

**Discussants.** George Spaeth and Felipe Medeiros.

**Session 3. Combination of Functional and Structural Tests**

**Participant.** Felipe Medeiros.

**Discussants.** Murray Fingeret, Chris Johnson, Christophor Girkin, David Greenfield, Jeffrey Liebmann, Michael Patella, and Linda Zangwill.

**Session 4. IOP Parameters as Outcome Measures**


**Discussants.** Douglas R. Anderson, Jeffrey Liebmann, Felipe Medeiros, and Anthony Realini.

**Session 5. Quality of Life: Parameters and Safety**

**Participants.** Rohit Varma, Anne Coleman, William Boyd, and Eva Rorer.

**Discussants.** Leslie Hyman and William Boyd.

**Session 6. Design and Endpoints for Glaucoma and Postmarketing Surveillance**

**Participants.** Gary Novack and Rhea Lloyd.

**Discussants.** Anne Coleman, David Greenfield, Leslie Hyman, and Rohit Varma.

**BACKGROUND**

Important issues that surround endpoints in clinical trials of glaucoma drugs include establishing and validating new parameters for glaucoma diagnosis and detection of progression, assessing the degree of structural and functional involvement, ascertaining correlations between structural and functional loss, predicting which level or kind of glaucomatous vision loss eventually affects a patient’s quality of life (QOL), and validation of equipment and technology for assessing involvement.

The NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium helped identify topics that should be addressed by the scientific and medical community and the requirements that must be met for presenting new drugs to the FDA for approval.

The meeting highlighted what is known about glaucoma and important questions that currently exist. The discussion was in the context of structural changes in the optic disc and RNFL, functional changes related to visual field loss, devices for detecting glaucoma and disease progression, the role of IOP and ocular perfusion pressure in glaucoma, QOL issues related to early and later visual field loss, QOL measurement tools, and postmarketing surveillance of glaucoma drugs and devices. This article presents some of the issues and attempts to show...
where attention is needed to advance new pharmacotherapies to the FDA for approval.

Topics included the need for industry-wide criteria for assessing glaucoma and disease progression, as well as the importance of defining endpoints in glaucoma clinical trials based on evidence of their impact on structural and functional parameters.

**Structural Parameters as Outcome Measures in Glaucoma Clinical Drug Trial Design**

Whether the FDA would consider a certain structural feature to be a particularly suitable endpoint in tests of a glaucoma neuroprotective drug was discussed. Glaucomatous changes in the optic nerve and peripapillary RNFL include focal or diffuse narrowing of the neuroretinal rim width, loss of peripapillary RNFL, increased excavation of the optic cup, presence of a β-zone of parapapillary atrophy, and hemorrhage of the optic disc.

What imaging technology or technologies would generate the most reproducible, objective, and quantifiable measures? Several are available: stereoscopic optic disc photography; confocal scanning laser ophthalmoscopy (CSLO) of the optic disc; scanning laser polarimetry of the RNFL (GDXVCC; Carl Zeiss Meditec, Dublin CA); and optical coherence tomography (OCT) of the RNFL.

And what measurements from which technologies would indicate efficacy?

The FDA has not included structural measurements as a basis for approval of glaucoma drugs and devices. “We are not there yet,” said Wiley Chambers, although the FDA does expect to use structural measures for evaluating new ophthalmic drugs and devices in the future, pending demonstration that such measures can predict clinically relevant functional outcomes.

The FDA has used functional endpoints (i.e., visual field, color vision, visual acuity, contrast sensitivity) for evaluating new drugs and devices for glaucoma.

**Some of What We Know about Structural Parameters**

Available information on structural measures in glaucoma is plentiful, but it has not been sufficiently evaluated and classified to answer questions about which measure or measures would be the best for predicting clinically relevant functional outcomes.

The following represent some of what we know about structural parameters in glaucoma.

Very little has been published about the rate of glaucomatous structural change. There are no uniform criteria for defining progressive structural events or for measuring the rate of tissue loss, and this deficiency makes it difficult to compare study results.

The World Glaucoma Association Consensus on Glaucoma Diagnosis has recommended to clinicians that they use digital imaging (preferably in conjunction with stereoscopic optic disc photography) to improve evaluation of the optic nerve and RNFL. The Ophthalmic Technology Assessment Committee of the American Academy of Ophthalmology similarly acknowledged that advances in digital imaging and related software make the use of digital imaging increasingly relevant.

Digital imaging (also referred to as optical imaging) of the optic disc and RNFL provides detailed representations and quantitative information about normal and glaucomatous structures of the eye. It has the potential to identify statistically significant change that is greater than known variability and may be able to provide automated estimates of the rate of change. Images obtained with digital technologies can be highly reproducible and therefore applicable in clinical practice and trials.

Imaging technologies are limited in their ability to detect optic disc hemorrhage, which is a risk factor for development and progression of glaucomatous optic neuropathy. Disc hemorrhage still is recognized best by clinical observation or review of optic disc photographs.

Measurements based on digital imaging technologies vary across manufacturers. This variation has presented a problem in standardizing data for comparing research results from different studies. Moreover, the hardware of various imaging devices has not been stable, and each succeeding new generation of an instrument generally has not been compatible with earlier versions. Rapid improvements in the technologies and their introduction into clinical practice without appropriate validation have also contributed to the lack of longitudinal studies with results that can be compared across time and researchers.

In some patients, digital imaging is capable of detecting changes in the optic disc earlier than is standard automated perimetry (SAP), a functional test that is currently the FDA benchmark for evaluating the efficacy of putative neuroprotective therapies.

**Key Issues**

- What is the timeframe for normal disease progression? Is there only one route to disease progression?
- What is the precise relationship between a structural change in the optic nerve (optic disc and RNFL) and visual field loss? Can a structural change in an individual with suspected or existing glaucoma predict the development of visual field loss? Does the location of the structural change correspond to the location of the functional change? Will this knowledge have an impact (benefit) on the QOL of patients?
- What is the most meaningful type of analysis for studying change in glaucomatous eyes? Event-based (compared with a baseline value) analysis? Trend-based (over time) analysis?
- What defines clinical significance for structural change?

Wiley Chambers of the FDA CDER told the meeting attendants that for structural measures to be used, the agency needs data to support that structural measures can predict clinically relevant functional change. Functional endpoints are used quite simply because visual function is critically important to every patient and because it can be measured.

Questions Dr. Chambers suggested that researchers consider are: (1) whether structural measures are more consistent and less variable than visual function measures; (2) whether there is a strong correlation between a structural measure and predictability of current or future visual function; and (3) whether the new approach will be beneficial to patients.

As the first step in identifying suitable structural methodologies, it was suggested that the methodology that would yield reproducible, objective, and quantifiable measures of clinically significant structural change or would be predictive of it has to be determined. As a second step, how much change is clinically significant in terms of function has to be established. In other words, it is necessary to prove that structural change has occurred, that the structural change is predictive of a functional change, and that progressive change will affect patients in their daily lives.

Third, it must be determined how long a structural change has to be present to cause a change in visual function. Which changes correlate highly with the ability to predict deficits in visual function? The final step is validation that the structural measure will perform as expected.
FUNCTIONAL PARAMETERS AS OUTCOME MEASURES IN GLAUCOMA CLINICAL DRUG TRIAL DESIGN

Tests that assess the functioning of the optic nerve are used in clinical practice and clinical trials to evaluate the extent of optic nerve damage from glaucoma and the progression of disease. The current gold standard for detecting optic nerve disease in glaucoma is the visual field test SAP. Defects in the visual field represent retinal ganglion cell dysfunction or loss. The pattern of the defects helps distinguish glaucoma from other possible visual disorders.

Perimetry frequently detects changes in visual function before patients become aware that their vision is affected. This makes perimetry an important tool for diagnosing and quantifying the progression of disease as well as for monitoring the ability of treatments to prevent additional ganglion cell dysfunction or loss.

As visual field testing is subjective, there generally is considerable variability in functional measures. Advantages of SAP include standardization of the testing procedure from test to test and among different locations. With SAP, there is the ability to compare test results to normative data, integrate data from multiple study centers, and perform statistical analyses on groups of patients or even individuals.

Newer functional tests for evaluating the visual field have been introduced. Among them are short-wavelength automated perimetry (SWAP), frequency-doubling technology (FDT) perimetry, motion perimetry, flicker perimetry, flicker-defined form (edge) perimetry, multifocal pattern electroretinography, multifocal visual evoked potential perimetry, pupil perimetry, high-pass resolution perimetry (HPRP), rarebit perimetry, and pattern-discrimination perimetry. Other types of psychophysical tests, such as contrast sensitivity and color discrimination, also have been studied.

Some of What We Know about Functional Parameters and Functional Perimetry

In clinical practice, a confirmed and significant glaucomatous change in any visual function test indicates potential disease progression. SAP is the most widely available, documented, and accepted perimetric measure for assessing visual function. Most other tests are commercially unavailable, have a limited dynamic range, or are difficult to use. Often, the results do not correlate well with those of SAP. SWAP, a test of chromatic (blue-yellow) perimetry, and FDT (Matrix; Carl Zeiss Meditec, Inc.), a test of temporal perimetry, are two possible exceptions, but still have limited data, particularly for longitudinal testing.

The most meaningful results of any of these functional tests are achieved by testing the patient frequently over time. There is no agreement about what constitutes a clinically significant change in visual function in patients with glaucoma.

There is no universally established approach for estimating future clinical progression of glaucoma. Predictive models are in their early stages. These models may ultimately pinpoint future glaucomatous optic nerve damage based on current locations of visual field deficits and past rate of progression. Adding variables such as age, IOP, and central corneal thickness may improve the predictive models.

The estimation of progression rate in glaucoma is important. Knowing progression rates will help direct treatment to the patients at the right time, when it is possible to prevent significant vision loss. Estimates of progression are extremely difficult because of variability within each patient (sometimes referred to as long-term fluctuation) and among patients. Trend analysis or event analysis may shed some light on progression rates in glaucoma. In trend analysis, the rate of change of the visual field is measured and the statistical significance of that rate is calculated. In event analysis, the first few visual fields in a series are used as a baseline and then compared to subsequent visual fields to determine whether change has occurred.

An advantage of trend analysis is that it provides information about rates of change, but it requires several reliable tests to determine a statistical trend. Event analysis generally requires fewer tests but gives relatively little information about rates. Furthermore, there is no consensus about which event to use as a standard.

The synchronicity of functional and structural changes in glaucoma, assuming it exists, is not established.

Key Issues

- Is any functional test superior to SAP? Might SWAP and FDT, which sometimes identify glaucomatous changes earlier and in different patients than does SAP, offer advantages?
- Might the various functional tests be assessing different characteristics of cell pathology or even different types of retinal ganglion cells? Might they perform better than SAP at particular stages of disease?
- Can changes in function in glaucomatous eyes be translated into changes in structure and vice versa? Can one inform the other and predict rate of progress of visual disability?
- How would variables such as the age of a patient, family history of glaucoma, region of visual function loss, and comorbidities influence clinical significance in trials of new drugs?
- What endpoint or endpoints should be pursued in clinical trials for measuring the efficacy of new glaucoma treatments?
- If nonreversible visual function loss is documented in a patient enrolled in a clinical trial, is there reason to await the development of clinically significant loss for it to qualify as an endpoint?
- What can be done now with the information we have to establish reliable endpoints that will provide a benefit to patients in terms of new treatments and improved visual outcomes?

From the perspective of the FDA CDER, represented by Martin Nevitt, MD, the levels of functional change indicated by an endpoint would have to represent clinical findings that most clinicians would agree is significant clinically. Different endpoints may be pursued in glaucoma trials but the trial sponsor would have to justify the clinical relevance.

Dr. Nevitt stated that for the indication for the treatment of glaucoma, as opposed to IOP reduction, a product under evaluation by the FDA would have to demonstrate, as a functional endpoint, an effect on progression of the disease (e.g., currently, visual field progression). Visual field changes may be acceptable as a clinically relevant primary endpoint provided a between-group difference in field progression is demonstrated. The progression of visual field loss will be suspected if five or more reproducible points, or visual field locations, have significant changes from baseline beyond the 5% probability levels for the glaucoma-change-probability (GCP) analysis.

Alternatively, visual field progression is suspected if the between-group mean difference in threshold for the entire field is statistically and clinically significant. This is often at least 7 dB on more than one examination. According to Dr. Chambers, “Seven decibels would be a loss that everyone would believe is a clinically significant difference.” He went on to say that less than 7 dB could also be clinically significant; data are just not currently available to support the lower number.

Another possible clinically relevant primary endpoint for glaucoma trials would be a change in color vision. The amount of change would have to be statistically significant using a validated scoring system such as the Farnsworth-Munsell 100 Hue Test.
Dr. Nevitt emphasized that it is premature to use change in the nerve fiber layer/optic disc as a surrogate for change in the visual field. They cannot be used interchangeably until both macroscopic and microscopic correlations between the two are established.

Therefore, according to the discussants, it is the responsibility of the glaucoma research community to amass functional data to establish endpoints that will be acceptable to the FDA. This may involve individual tests or combinations of functional tests (e.g., SAP, SWAP, and FDT), with the results treated in a weighted fashion, perhaps with the stage of disease factored in, for arriving at a composite endpoint in clinical trials of a new drug therapy. The FDA, says Dr. Nevitt, is willing to discuss and, if appropriate, sign off on predefined functional endpoints before clinical trials begin. If the predefined endpoints were achieved, the FDA would then consider these endpoints in reviewing products for approval.

**Combined Structural and Functional Parameters as Outcome Measures in Glaucoma Clinical Drug Trial Design**

Structural and functional parameters, separate from each other, as endpoints in clinical trials of new glaucoma drugs were discussed in the two preceding sections of this report. This portion of the report addresses the question of whether a combination of structural and functional tests could more effectively detect glaucoma and/or glaucomatous progression than could the two alone.

Most clinicians and researchers agree that the ideal answer would be yes, assuming that different diagnostic tests provide unique (not redundant) and clinically relevant information. Although they used different methodologies for assessing the visual field and optic disc, there is evidence to this effect from two clinical trials, the Ocular Hypertension Treatment Study (OHTS) and the Early Manifest Glaucoma Trial (EMGT). In the OHTS, the first detectable changes were more often identified in structure while in the EMGT they were more often identified in function. Several factors may account for these differences, including different methodologies, patient populations, and stage of the disease.

Additional evidence for unique findings based on structural versus functional parameters comes from a longitudinal study comparing detection of glaucomatous progression in patients with early glaucoma, by using scanning laser tomography and SAP. Patients were observed for a median of 5.5 years. Of those:

- 27% showed no progression with either technique;
- 40% showed progression based on evidence from scanning laser tomography only;
- 4% showed progression based on evidence from conventional perimetry only; and
- 29% showed progression with both techniques.

The researchers concluded that glaucomatous disc changes determined with scanning laser tomography appear earlier than perimetric changes. Furthermore, they found that most patients with field changes also had disc changes, a finding that was not true in the reverse. Fewer than half of those with disc changes also had field changes. The same pattern has emerged in examinations of structural changes with other imaging instruments such as scanning laser polarimetry. Many patients have observable progression initially only by structure. In other words, structure and function are not completely redundant, at least not measurably, when using today’s technology.

Therefore, it would appear that, by combining structure and function, it may be possible to detect glaucoma and progression of glaucoma in more patients earlier. The question remains as to the clinical relevance of changes in tests of structure as they relate to function. An understanding of the relationship between structure/function/clinical relevance will help us design better ways of combining structure and function to detect glaucoma or progressive disease.

**Some of What We Know about the Synergy of Tests of Structure and Function**

A proportion of patients show significant changes in function without statistically significant changes in structure. Conversely, a proportion of patients show significant changes in structure without statistically significant changes in function.

Baseline abnormalities in structural tests in patients with glaucoma are predictive of worse functional outcomes. And functional changes at baseline also are predictive of structural changes.

A combination of structural and functional tests may diagnose and detect more patients as having progressive glaucoma.

**Key Issues**

- How are longitudinal changes in structural tests related to real-world functional loss for patients? Do they occur in parallel? Serially?
- What are the best combinations of available structural and functional tests for detecting disease and monitoring progression? Might one test be better at a particular stage of disease than another? For example, in patients with advanced disease it is harder to detect disc progression structurally. For them, tests of functional capacity might more accurately track progression than in patients with early glaucoma for whom only structural change might be evident.
- Because in many patients a detectable (by current technologies) structural change precedes a detectable functional change, would it be reasonable to rely on the structural test instead of the functional test?

A point that was revisited in the session was the observation raised by Mae E. Gordon, PhD, of the OHTS (Ocular Hypertension Study) Group, that in a patient with advanced cupping it is difficult to detect disc progression structurally because of a ceiling effect. For assessing these patients, using functional measures makes obvious sense. However, because structural changes in the optic disc and RNFL appear to precede functional changes during the earlier stages of disease, structural outcomes (or a combination of structural and functional outcomes) may serve as better endpoints early on.

**IOP Parameters as Outcome Measures in Glaucoma Clinical Drug Trial Design**

Elevated IOP is a known risk factor for glaucoma. The importance of reducing IOP for slowing disease progression has been confirmed in major clinical trials including the Ocular Hypertension Study, Early Manifest Glaucoma Trial, Collaborative Initial Glaucoma Treatment Study, and European Glaucoma Prevention Study. According to Dr. Chambers, IOP lowering is not sufficient for FDA approval of new glaucoma drugs. Proof of IOP lowering (in the absence of proof of change in the structural or functional course of the disease) yields approval for IOP lowering only and not for treating glaucoma.

The measurement of IOP is influenced by several factors including time of day, corneal thickness, corneal biomechanics, blood pressure, and even prior corneal surgery. Sessions at this NEI-FDA symposium addressed several of these influences in relation to the use of IOP as a potential endpoint for glaucoma drug approvals. Also discussed was the role of the nonselective β-adrenergic receptor antagonist (i.e., timolol) and the prostaglandin analogues (e.g., latanoprost) as a standard of
comparison for proposed new drugs for lowering IOP. The FDA explained its position relative to IOP as an endpoint and the responsibility of study sponsors to prove that IOP is a suitable endpoint.

Some of What We Know about IOP

Information about IOP relative to glaucoma is growing, but much is still largely unquantified. What follows is some of the current knowledge about IOP and glaucoma and areas in which researchers see a need for additional research, to understand the full impact of IOP.

Elevated IOP is a positive risk factor for the development of glaucomatous optic nerve damage and visual field loss.

Lowering IOP slows the rate of progression of glaucomatous optic nerve damage, regardless of the stage of the disease.

IOP fluctuates during the day and night. It often is higher at night when blood pressure is lowest and it naturally spikes on awakening. The term fluctuation is used to refer to changes in IOP during a 24-hour period. Patients with higher IOP tend to have greater fluctuations.

Variation in IOP should be used to refer to pressure measurements that are recorded from one clinical visit to the next. There is no consensus on how variation (or fluctuation) affects the progression of disease.

There is no current measurement device for tracking IOP continuously in clinical practice. Furthermore, IOP measurements are affected by corneal elasticity, corneal thickness, sometimes by previous eye surgeries, and more. Therefore, true IOP in most patients is unknown.

The drug timolol reduces IOP and has been used as a gold standard for efficacy of other IOP-lowering therapies. More recently, prostaglandin analogues, a class of more effective IOP-lowering drugs, have been accepted as alternatives for comparison with other IOP-lowering therapies.

Key Issues

There are many unknowns about IOP in glaucoma and its utility as an endpoint in new drug trials. Several were raised in presentations and discussion:

- Which IOP parameters (i.e., mean IOP, peak IOP, fluctuation in IOP, variation in IOP) might be appropriate endpoints for clinical drug trials? What is the predictive value of each in terms of functional and structural outcome?
- How do different pharmacotherapies compare with each other with respect to variation, fluctuation, and other characteristics of IOP?
- What is the therapeutic value of the relationship of baseline IOP to ending IOP?
- Are all degrees and rates of increased IOP equally damaging at all stages of disease? Are variations and fluctuations in IOP damaging?

Dr. Chambers reminded the meeting attendees of a critical feature for the FDA CDER in considering new IOP-lowering (or any other) drugs: benefit-to-risk ratio. The benefit is determined by efficacy in clinical trials. The FDA makes a calculated assessment of risk based on evidence from the clinical studies.

The current standard (benchmark) for proposed IOP-reducing agents (separate from glaucoma drugs) is equivalency to one of four FDA approved products:

- timolol maleate ophthalmic solution;
- latanoprost ophthalmic solution, a prostaglandin analogue;
- bimatoprost ophthalmic solution, a prostaglandin analogue;
- and travoprost ophthalmic solution, a prostaglandin analogue.

Each is known to lower IOP. The effect is reproducible and predictable in most people. The risks are known and, with appropriate patient selection to avoid adverse cardiorespiratory events, the benefit-to-risk ratio is positive. They can be used as standards for comparison to new drugs being proposed for use as primary therapies or to drugs that are additive to another IOP-lowering product in a different class.

Timolol lowers IOP approximately 5 to 7 mm Hg in patients with baseline IOP between 21 to 26 mm Hg. It does so by decreasing production of aqueous humor. On the risk side of the calculation, timolol decreases heart rate and may impair respiratory function.

The prostaglandin analogues lower IOP approximately 6 to 8 mm Hg in patients with baseline IOP between 21 to 26 mm Hg. They work by increasing aqueous outflow. Risks include iris and skin hyperpigmentation, intraocular inflammation, and macular edema in predisposed patients.

In comparisons to these benchmarks, the FDA looks for the benefits of new IOP-lowering drug products to outweigh the risks:

- If the benefit is greater than the current standard, risk may be greater, the same or less.
- If benefit is the same as the current standard, the risk should be the same or less.
- If the benefit is less than the current standard, the risk should also be less.

Dr. Chambers emphasized that, for new drug approvals, the FDA differentiates between a glaucoma indication and an IOP-lowering indication. In other words, an IOP-lowering drug does not have to show an effect on the disease process.

Ideally, at the outset, when a sponsor is planning to seek approval for a new drug, that sponsor should approach the FDA with a proposal for a clinical trial. The FDA stated that they are “always open to considering [proposals for] any kinds of new endpoints.” Adding, “But the burden is on [the sponsor] for showing why this is important.” According to Dr. Chambers, “The issue always comes back to whether it is going to make a difference to a patient [in the real world]” and the benefit-to-risk ratio. Approval of a novel drug depends on review of all the data.

In answering whether the FDA would allow reductions in IOP to act as a surrogate for reduction in the loss of optic nerve axons or retinal fiber layer, Dr. Chambers made it clear that a sponsor who proposes a surrogate for study related to structure and function would have to provide proof of an existing relationship between the events. In other words, IOP as an endpoint for protecting the glaucomatous optic nerve is appropriate only if the relationship between IOP change and glaucomatous change in response to that drug can be quantified.

QOL Parameters as Outcome Measures for Glaucoma Clinical Drug Trials

The World Health Organization defines QOL as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment.”

The FDA, in draft guidance calls health-related QOL (HR-QOL) “a multidomain concept that represents the patient’s overall perception of the impact of an illness and its treatment.”
In ophthalmology, HR-QOL instruments are used to assess self-reported general and visual functioning of patients. Although many different instruments have been used for measuring QOL in patients with glaucoma (Table 1), the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) is the most widely used.

The decision to shorten the VFQ-51 was related to the length of time it took to administer. The shortened version, VFQ-25, has demonstrated the same internal consistency and test-retest reliability as the VFQ-51. It has been validated and used to show that people with eye disease and visual impairment have lower scores than do groups without eye disease or visual impairment.

A shortcoming of the VFQ-25 may be that there is little information about its inter-interviewer reliability or its ability to detect change in glaucoma.

The purpose of the current session was to examine the association between patient-reported QOL and glaucoma damage among adults with glaucoma; to discuss the FDA requirements for using QOL as endpoints in glaucoma clinical drug trials, and to understand what needs to be done to make QOL instruments acceptable to the FDA.

Some of What We Know about QOL Measures in Glaucoma

Studies examining the relationship between glaucomatous visual field loss and health-related QOL have found that a decline in visual field is associated with a decline in health-related QOL. The relationship between visual field loss and involvement in everyday activities is strictly monotonic (irreversible). Visual field loss, even at its earliest stages, affects QOL.

Driving is significantly affected by visual field loss in glaucoma. Risk of falling also increases greatly. A 3- to 4-dB difference in visual field loss is associated with a clinically meaningful 5-point difference in the NEI-VFQ driving subscale.

Loss in HRQOL scores for glaucoma participants was present in people with mild VFL and continuing through moderate to severe VFL.

Key Issues

- What degree of glaucomatous visual field loss is necessary for meaningful change in the ability of adults to function independently or complete vision-related tasks to become observable?
- What is the impact on QOL of peripheral vision loss independent of central visual impairment?
- What types of daily activities are affected by visual field loss?
- Glaucoma is a slowly progressive disease. How often, and at what intervals, would a QOL measure be administered for assessing change? Would it depend on stage of disease?
- What aspects of QOL are affected by different degrees of visual field loss?
- How does the location of visual field loss influence health-related QOL?
- Factors such as educational status and comorbidities affect outcomes on tests of health-related QOL. Adjustment must be made for these covariants in evaluating clinical and research-related outcomes.
- Most analyses are based on cross-sectional data. Caution should be exercised in drawing inferences about changes in QOL related to changes in visual field. Longitudinal studies will help in our understanding of the relationship over time.
- Few people with advanced visual field loss related to glaucoma have been included in health-related QOL studies. It is possible that the difficulties that affect them are different from those in patients with less-advanced disease.
- Available data are based on self-reports that do not provide an objective assessment of individuals’ activities.
- We do not know the ability of health-related QOL measures to predict change related to progression of glaucoma.
- QOL measures may be affected by age and sex. Furthermore, they may not correlate with product effect.

The position of the FDA CDER was presented by William Boyd, MD, clinical team leader in the FDA’s Division of Anti-infective and Ophthalmology Products. He reminded symposium attendees that the endpoints and levels of change cited in the FDA presentations are meant to represent a clinical finding that almost all clinicians would agree is a clinically significant change. He reiterated what earlier FDA representatives had said: Different endpoints may be pursued, but the trial sponsor would have to justify the clinical relevance of the endpoint(s); adequate justification of the different endpoint(s) would be an issue for review.

Subjective QOL measures for glaucoma could be directed at vision or at the general health of the patient. This alone, however, is unlikely to serve as the basis for product approval. Products proposed for the treatment of glaucoma would also have to demonstrate an acceptable risk-benefit ratio and be subjected to internal and external validation.

For internal validation, the QOL instrument must be shown to reliably and reproducibly quantify a patient’s health perceptions and/or his or her functional status. For external validation, the health perceptions and/or functional status measured by the QOL instrument must be shown to correlate to real clinical situations. For example, a person’s perceived ability to perform near-vision activity would have to be correlated to near vision function.

Dr. Boyd stated that QOL measures provide very useful supportive information. The FDA encourages their use in clinical trials. Whether they end up in product labeling depends on proper administration of the instrument, proper validation, and adequate statistical power to show differences between study groups. The FDA has drafted a document (Study Endpoints and Label Development [SEALD]) describing the requirements for internal and external validation. The VFQ-25 has not been adequately externally validated nor has it met all criteria for
validating instruments. The guidance document is available at the FDA Web site (www.fda.gov/cder/guidance/5460dft.htm).

Eva Rorer, MD, reported that the FDA was planning an open public meeting to discuss postmarket experience with LASIK, which was to include a discussion of QOL. Dr. Rorer is a chief ophthalmic medical officer in the Office of Device Evaluation at the Center for Devices and Radiologic Health (CDRH). There have been complaints from a small number of people that LASIK has adversely affected QOL. She also reported that the FDA is discussing possible appropriate instruments for a multicenter clinical trial to investigate QOL after LASIK and that the FDA and NEI are collaborating in a study of ways to decrease the amount of time and money associated with administration of QOL instruments. A pilot study is under way to validate computer administration of vision-targeted QOL instruments.

The CDRH recommends the inclusion of QOL measures in clinical trials and would consider QOL as a primary endpoint if it were combined with other endpoints. They also recommend the use of PROs, or patient report outcome measures. A PRO is a measurement of any aspect of a patient’s health status that is reported directly by the patient without interpretation by a physician or anyone else. The CDRH further encourages the development of validated QOL instruments that focus on impact of treatment with glaucoma devices.

Given the unique qualities of subjective questionnaires like the VFQ-25 and the challenges envisioned in interpreting the totality of evidence in a glaucoma clinical drug trial, the FDA expressly recommended that sponsors contact them for input about using QOL measurement instruments as drug trial endpoints. In fact, the FDA is willing to discuss all drug trials and recommends meetings between sponsors and the agency from the pre-IND phase onward.

### Table 2. First-of-Their-Class Drugs Approved for Lowering IOP

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA NDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine insert</td>
<td>1974</td>
</tr>
<tr>
<td>Timolol</td>
<td>1978</td>
</tr>
<tr>
<td>Dipivefrin</td>
<td>1980</td>
</tr>
<tr>
<td>Pilocarpine Gel</td>
<td>1983</td>
</tr>
<tr>
<td>Apraclonidine</td>
<td>1987</td>
</tr>
<tr>
<td>Dorzolamide</td>
<td>1994</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>1996</td>
</tr>
</tbody>
</table>

NDA, new drug approval.

Postmarketing Surveillance of Glaucoma Drugs

This session was divided into two discussion topics: efficacy and safety.

#### Efficacy

Gary Novack, MD, pointed out that worldwide, approvals for pharmacotherapies for glaucoma and ocular hypertension are based on ocular hypotensive efficacy, which is in turn based on the supposition that ocular hypotensive efficacy is a surrogate for reduced risk of progression of glaucomatous disease. Shown in Table 2 are examples of the first in class approvals of glaucoma pharmacotherapies by the FDA.

Drs. Novack and Lloyd confirmed that currently, to obtain FDA approval for a drug that controls elevated IOP, the sponsor must demonstrate 3 months of drug efficacy against a control. Equivalence to an active control is defined as having a confidence interval of between 1 and 1.5 mm Hg at all time points. The sponsor is further required to show 12-month safety data based on at least 100 patients using the intended dose or higher. The primary efficacy endpoint required by the FDA is mean IOP.

The issue was raised of a sponsor being asked to continue to monitor enrolled individuals over time to watch for progression. If the sponsor desires an indication for glaucoma progression per se, then those studies are much larger and longer and should be planned to determine progression way from the outset. From the sponsor’s point of view, postmarketing research presents many problems, for example:

- Clinical trial sponsors would have to enroll many more participants to maintain statistical power, as subjects drop out of studies over time.
- The cost of conducting and reporting on the studies could be prohibitively high for both researchers and participants.
- Continuing the study would put a burden on institutional review boards.
- Ethical concerns for continuing control groups receiving placebo treatment must be considered.
- Confounding variables increase as a patient ages, which can interfere with assessment of IOP and visual function.

#### Safety

Recognizing the limitations of clinical trials including their small size relative to the number of people who will be using a drug, the FDA has developed approaches for monitoring the safety of approved drugs in patients for whom use is indicated on the label, in patients with other illnesses who are taking additional medications that might interact with the new drug, and in off-label use.

Many more people use a newly approved drug than the number of people on whom it is tested in clinical trials. Many of these users have other illnesses and are taking medications that may be affected by the new drug (or that may affect the new drug). Postmarketing surveillance could reveal rare adverse events or, on the positive side, could reveal additional indications for the new drug.

Although the FDA does not generally require clinical trials to be extended into the postmarketing period, they do have mandatory requirements for sponsors and manufacturers to report adverse events and have established an adverse-events reporting system called MedWatch (www.medwatch.gov). Ninety-five percent of reports to MedWatch come from manufacturers. The FDA studies MedWatch for new unlabeled adverse effects, increases in a labeled event or in its severity or specificity, new drug or food interactions, and newly identified at-risk populations. Safety evaluators also search the scientific and medical literature and public databases from groups like the World Health Organization and foreign regulators, looking for similar reports.

The FDA has mechanisms for monitoring the “life cycle” of drugs they have approved and for dealing with significant adverse events detected in the postmarketing period. The sponsor could be asked to make labeling changes. Letters may be sent to healthcare providers describing additional risk. Risk management plans and programs are sometimes initiated. In extreme cases, a product’s approval is withdrawn.

Postmarketing safety in ophthalmics raises fewer concerns than in many other fields, perhaps because the systemic absorption of ophthalmic drugs can be minimized. Still, the FDA Office of New Drugs is formally addressing, with safety evaluators and others, potential postmarketing surveillance issues. Many are only as good as voluntary reporting of adverse events from patients and clinicians to the drug manufacturers or directly to MedWatch, which the FDA assiduously evaluates.
SUMMARY

In this meeting, glaucoma researchers learned from the FDA about the agency’s willingness to consider additional outcome measures, especially related to optic nerve and RNFL structure and function, in the approval process for new glaucoma drugs. The FDA clarified its position saying that it is the responsibility of the research community to demonstrate that structural measures correlate with clinically relevant functional measures.

Follow-up meetings were proposed to establish and agree on definitions and standards for structural changes in the glaucomatous optic nerve, functional changes in vision, for a combination of the two, and for analysis and reporting of findings. Meetings were also proposed for discussing new technologies and for making recommendations that would guide industry, researchers, and practitioners.

For guidance, the FDA pointed to draft documents that reflect its current thinking. However, according to Dr. Chambers, the FDA “does not … know all the ways to study a particular product.” In other words, guidance documents are not intended to represent the only acceptable methodologies or endpoints. It is the responsibility of researchers to select instrumentation and parameters and to demonstrate to the FDA that their findings can reliably predict the clinical, real-world safety and efficacy of a new drug. The FDA encourages sponsors of glaucoma clinical trials to propose new clinical endpoints and to discuss these with the FDA at a very early phase of research planning.

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References