# The FDA's Role in Shaping the Future of Glaucoma Care

## Navigating the approval of new glaucoma drugs.

**By Rhea Lloyd, MD, and Sonal Wadhwa, MD**

The goal of the FDA is to ensure that safe and effective drugs are available to the American public. New drugs enter the US market after the FDA's approval of a New Drug Application (NDA) or Biologic License Application. This review process requires the collaboration of an interdisciplinary team of clinicians, scientists, and regulatory personnel who are ultimately responsible for recommending the approvability of a drug based on defined requirements, including the drug's risk/benefit profile, quality and purity, and ability to be labeled effectively.[1]

### THE PHASES OF DRUG DEVELOPMENT

To fulfill the FDA's mission to ensure that marketed drug/biologic products are safe and effective, these products are usually tested in nonclinical trials and in three phases of human clinical trials. A primary goal of nonclinical studies is to describe the drug's basic pharmacology and pharmacokinetics as well as to evaluate the basic toxicology and early concepts of activity. Initial nonclinical investigations are performed in various suitable animal models.

Building on the information gained in the nonclinical program, the phase 1 clinical studies begin human dosing of the drug product. In the development of IOP-lowering or glaucoma drugs, phase 1 trials to test for tolerability can be conducted in healthy individuals, ocular hypertensive patients, or patients with primary open-angle glaucoma. The goal of phase 2 trials is to determine the minimum dose that is maximally effective in the target population. The goal of phase 3 trials is to replicate the safety and efficacy of the drug in at least two adequate and well-controlled independent trials.[2]

### ENDPOINTS

For trials of a new drug product in patients with glaucoma, one endpoint has usually been pursued: the treatment of elevated IOP or the treatment of glaucoma. Although not synonymous with glaucoma, elevated IOP has been a commonly treatable condition in patients with the disease. Demonstrations of a drug product's efficacy are recommended to include evidence of statistical significance and clinical relevance.

Efficacy trials can be designed to show superiority or equivalence to an acceptable active control. Superiority of the test product would be demonstrated in comparison to a vehicle or an active control. Acceptable active controls are timolol maleate ophthalmic solution 0.5% dosed twice a day or latanoprost ophthalmic solution, bimatoprost ophthalmic solution, or travoprost ophthalmic solution administered once a day in the evening. Equivalence is defined as the two-sided 95% confidence interval's being less than 1.5 mm Hg at each direct group comparison measured multiple times over a 3-month period and being less than 1 mm Hg for the majority of direct group comparisons. The time points include both the peak and trough efficacy times for both the test and control agents at baseline and at weeks 1 (or 2), 6, and 12.[3]

Unlike the treatment of elevated IOP, for an indication for the treatment of glaucoma, a product is expected to demonstrate an effect on the progression of the disease process (eg, visual field progression after at least 5 years of treatment). Visual field changes would be acceptable as a clinically relevant primary endpoint, provided a between-group difference in field progression were demonstrated. For example, a 24-2 full-threshold visual field might be considered to demonstrate progression if five or more reproducible points of the 52 nonblind spot visual field locations had significant changes ($P < .05$) from baseline beyond the 5% probability levels for the glaucoma change probability analysis. Alternatively, visual field progression might be considered significant if the between-group mean difference in threshold for the entire field demonstrated at least a statistically significant 7-dB change on more than one examination.

Other potential endpoints for the indication for the treatment of glaucoma could be irreversible changes to the

optic disc or nerve fiber layer, but the amount of change that is clinically relevant is currently unknown. In other words, the minimum amount of nerve fiber layer loss that consistently causes glaucomatous progression has not yet been determined.

## FILING AN NDA/REVIEW CLOCKS

Once an application is submitted, the FDA is expected to complete the review and make a regulatory decision. A priority review is given a 6-month deadline from the date when the application is received. Priority review is granted for an application that appears to represent a significant therapeutic advance with respect to available therapies by providing (1) greater effectiveness or safety, (2) a substantial reduction of a treatment-limiting drug reaction, (3) a documented enhancement of patients' compliance, or (4) safe and effective treatment of a new subpopulation. All other applications are granted a standard review and are given a 10-month review clock.

## TYPES OF ACTIONS

After a full and complete review of the NDA, the Agency makes its regulatory decision. The regulatory action may take two forms: approval or complete response. An approval action means that the Agency has determined that the drug has demonstrated safety and efficacy in adequate and well-controlled trials and may be marketed in the United States. A complete response indicates that deficiencies in the application need to be resolved prior to approval.

## PHASE 4 TRIALS

Drug development does not necessarily end with the FDA's granting marketing approval for a drug. The Agency may request that the applicant provide additional information about the drug's safety or efficacy after approval. Often, these postmarketing commitments or postmarketing requirements are postapproval studies or investigations required as a condition of approval, but they do not preclude marketing of the product. Phase 4 commitments are binding agreements between the applicant and the FDA, and they include a timeline for the completion of the studies.

## SUMMARY

Ensuring that safe and effective drugs are available to the American public requires the collaborative effort of scientists within the FDA who interact with colleagues in the pharmaceutical industry, usually over a period of years. When an NDA or Biologic License Application is filed, the reviewers conduct a full and thorough review of all of the data presented. The process concludes with all reviewers weighing the drug product's risks and benefits regarding safety and efficacy so that a regulatory decision can be made.

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1. US Food and Drug Administration. Information on the Development and Approval Process for New Drugs. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm. Updated August 20, 2010. Accessed July 7, 2011.
2. Code of Federal Regulations, Title 21, Part 31, section 126 (21CFR31.126).
3. Temple R. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, eds. *Clinical Measurement in Drug Evaluation.* Hoboken, NJ: John Wiley & Sons; 1995:3-22.

# How the Center for Devices and Radiological Health works to facilitate innovation and maintain public health.


**By Malvina Eydelman, MD, and Robert Lee Kramm, MD**

The substantial need for effective treatments of glaucoma, patients' poor adherence to IOP-lowering drug therapy, and a large and expanding patient population[1,2] have spurred significant growth in the development of glaucoma devices. In order to speed innovation, it is imperative for the glaucoma community to understand where and how the FDA fits into the picture.

Ensuring the safety and effectiveness of medical devices is under the purview of the FDA's Center for Devices and Radiological Health (CDRH). An instrument or machine is considered to be a device if (1) it is intended for use in the diagnosis of or in the cure, mitigation, treatment, or prevention of disease and (2) it affects the structure or function of the body, does not achieve its primary intended purposes through chemi-

**TABLE. RISK-BASED CLASSIFICATION OF MEDICAL DEVICES**

| Class | Risk | Regulatory Requirements | Examples |
|---|---|---|---|
| Class I | Low | General controls | Visual acuity charts, perimeters, and manual surgical instruments |
| Class II | Moderate | General controls and special controls | SLO polarimetry, CSLO topography, OCT slit lamps, tonometers, glaucoma implants for the refractory population, and lasers used for the treatment of glaucoma (such as argon lasers for trabeculoplasty) |
| Class III | High | General controls and premarket approval | Glaucoma implants (for the nonrefractory population) and viscoelastics |

*Abbreviations: SLO, scanning laser ophthalmoscopy; CSLO, confocal scanning laser ophthalmoscopy; OCT, optical coherence tomography.*

cal action, and is not dependent upon being metabolized for the achievement of its intended purposes.

## THE CLASSIFICATION OF DEVICES

The FDA uses a tiered, risk-based classification of medical devices in determining the regulatory requirements for the premarket review process. Each generic type of device is assigned to one of three regulatory classes, each with distinct regulatory requirements (Table).

General controls are the baseline regulatory requirements that apply to all three classes of medical devices. The provisions of general controls include the prohibition of adulterated/misbranded devices, manufacturer registration and listing requirements, good manufacturing practices, and record keeping.

Class I devices are of low risk. Most are exempt from premarket notification (510[k]).

Class II devices are moderate-risk devices for which the FDA has determined that special additional controls are necessary. These may include special labeling requirements, mandatory performance standards, and postmarket surveillance requirements. Manufacturers intending to market a new class II glaucoma device will need to obtain FDA marketing clearance through the premarket notification (510[k]) process. A premarket notification 510(k) must demonstrate that the device to be marketed is at least as safe and effective as (ie, substantially equivalent to) a legally marketed device (as described in 21 CFR 807.92[a][3]).

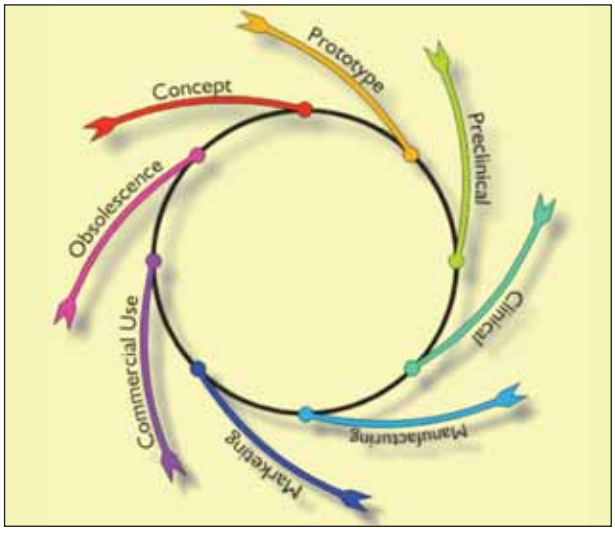


**Figure 1. The FDA's involvement in the Total Product Life Cycle.**

Class III devices are those for which insufficient information exists to ensure safety and effectiveness solely through general or special controls. Premarket approval is the required process of scientific review for class III devices. The applicant must receive FDA approval prior to marketing the device in the United States, based on a determination that the premarket approval application (PMA) contains sufficient valid scientific evidence to provide a reasonable assurance of safety and effectiveness for the device's intended use(s).

## INVESTIGATIONAL DEVICE EXEMPTION

In addition to reviewing premarket applications for glaucoma devices, the FDA is responsible for the regulatory oversight of clinical studies for investigational devices that pose a significant risk. An investigational device exemption (IDE) allows the sponsor of this application to clinically study the investigational device for an indication for which the device has not received prior marketing clearance or approval.

An IDE applicant to the FDA must submit an investigational research plan that describes the research design and analytical methods to be used. The FDA and sponsors often engage in extensive communication of research studies to support any future claims of safety and effectiveness. An IDE study cannot proceed until the IDE is approved by the FDA and an Institutional Review Board.

## THE FDA's PROMOTION OF INNOVATION

The FDA's mission includes advancing public health by helping to speed innovation. CDRH's staff actively collaborates with industry and investigators on the development of rigorous clinical studies that will provide adequate data

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on safety and effectiveness to support the FDA's clearance or approval of glaucoma devices.

The FDA widely uses the pre-IDE process to interact with the sponsors of glaucoma device submissions. The pre-IDE process provides a means of gaining comments and feedback from the FDA on proposed studies intended to support a marketing application (whether or not an IDE is actually required). This allows for early interaction and minimizes delays in getting clinically useful devices to market.

In addition to addressing individual applicants' issues, CDRH invests significant resources into the development of standards and consensus for appropriate clinical trial designs for glaucoma devices. Some examples include the FDA's involvement in the American National Standards Institute standard for implantable glaucoma devices and Clinical Trial Endpoints Symposia[3-5] orchestrated by ARVO, two of which were dedicated solely to glaucoma.[4,5]

## TOTAL PRODUCT LIFE CYCLE

CDRH is responsible for the total product life cycle of glaucoma devices (Figure 1). In addition to helping transform the concept for a new glaucoma device to a newly marketed device, the FDA monitors the performance of glaucoma devices in commercial use. To supplement the mandatory reporting of adverse events by manufacturers, the FDA relies heavily on voluntary reports from practicing physicians for alerts about any significant safety issues with devices on the US market. The FDA urges the glaucoma community to help protect public health by reporting device-related adverse events through MedWatch (http://www.fda.gov/medwatch/). ❑

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1. Friedman DS, Wolfs RC, O'Colmain BJ, et al; Eye Diseases Prevalence Research Group. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol*. 2004;122(4):532-538.
2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262-267.
3. Varma R, Richman EA, Ferris FL III, Bressler NM. Use of patient-reported outcomes in medical product development: a report from the 2009 NEI/FDA Clinical Trial Endpoints Symposium. *Invest Ophthalmol Vis Sci*. 2010;51:6095-6103.
4. Weinreb RN, Kaufman PL. The glaucoma research community and FDA look to the future: a report from the NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium. *Invest Ophthalmol Vis Sci*. 2009;50:1497-1505.
5. FDA and National Eye Institute. 2010 NEI/FDA Glaucoma Clinical Trial Design and Endpoints Symposium: Measures of Structural Change and Visual Function. Presented at: National Institutes of Health; September 24, 2010; Bethesda, MD. http://www.arvo.org/eweb/epoints10/pdf/AgendaCoursebook.pdf. Accessed August 1, 2011.