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Special Commentary: Food and Drug Administration and American Academy of Ophthalmology Sponsored

Developing Novel End Points for Premium Intraocular Lenses Workshop

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The pace of medical research and development, estimated at $85 billion in research and development by industry plus the National Institutes of Health in 2010 alone, has brought about significant breakthroughs in medical care in the United States. Yet, there has been widespread concern that this investment has not yielded novel product applications to the Food and Drug Administration (FDA) or the diffusion of innovative medical technologies into the marketplace. The factors slowing medical innovation and keeping devices from the hands of clinicians in this country are complex. The reasons range from the economic uncertainties and fluctuations in the past several years, the difficulties and complexities of the science governing product development, to the regulatory obligation to ensure the safety and efficacy of products reaching the marketplace. The environment for medical product development is complex, and multiple solutions and approaches are needed to improve the efficiency and throughput of the processes needed to bring products to fruition.

The landscape of intraocular lens (IOL) product development is a prime example of this complex ecosystem. This is a burgeoning area of innovation, with many breakthrough designs to address the increasing need of patients with cataract to achieve clearer vision across a range of viewing distances without the aid of spectacles. These "premium" designs, which correct more than the spherical error at distance, include multifocal, accommodating, toric, and phakic IOLs. The first premium IOL was approved in 1997, and as of the March 28, 2014 workshop there were 3 multifocal, 1 accommodating, 4 toric, and 2 phakic IOLs approved in the United States. Approximately 14% of cataract patients receive premium IOL implants.[1] Despite the recent increase in the number of premium IOL submissions to the FDA, information in FDA guidance documents and recognized standards is somewhat limited with regard to acceptable adverse event (AE) benchmarks and appropriate test methods that are applicable to particular premium IOL device types. As a result, the FDA evaluates premium IOL submissions on a case-by-case basis, with significant resources expended on repeat submissions and of limited benefit to the submissions of devices with similar technologic characteristics from other sponsors because of confidentiality issues. In addition, some premium IOLs have certain optical properties that may provide added benefit or confer increased risks to patients and may require different categorization and methods of evaluation.

On March 28, 2014, the U.S. FDA and the American Academy of Ophthalmology convened clinicians, researchers, industry representatives, and regulatory officials to discuss novel end points and assessment methods for premium IOLs. The main topic of this workshop was the current challenges in the assessment of innovative IOL designs, with a focus on end point methodologies used in evaluating IOL safety and effectiveness. Experts in subjects ranging from patient-reported outcomes (PROs) to objective measures of accommodation provided talks on the latest developments in the field. In the afternoon, participants engaged in breakout groups to discuss the pros and cons of various methods used to assess premium IOLs and obtain recommendations on the end points and the preferred approach to developing measures for the needed end points.[2] The primary goal of the workshop was to work collaboratively to improve the regulatory science for evaluating premium IOLs, which, in turn, will enhance the efficiency with which premium IOLs that have demonstrated a reasonable assurance of safety and effectiveness move through the regulatory process and become available on the U.S. market.

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Regulation of Intraocular Lenses

The FDA has the flexibility to calibrate its regulatory approach to the level of potential risk posed by new products. This risk-based paradigm is described by the device classification system,[3] which is based on the level of controls necessary to reasonably ensure the safety and effectiveness of the device. Because IOLs can present a potential unreasonable risk of illness or injury, these devices have been classified as class III, which is the most stringent regulatory category. Class III devices require submission of a premarket application with data to demonstrate a reasonable assurance of safety and effectiveness. Determinations of safety and effectiveness are based on considerations of the intended population, conditions of use for the device, probable benefit to health versus probable injury or illness from use, and reliability of the device. The FDA has worked with the American National Standards Institute (ANSI) and the International Organization for Standardization (ISO) to develop standards for IOLs. These FDA-recognized standards address nonclinical requirements and clinical study design and end points for IOLs[4] (Table 1). For IOL modifications, ISO Technical Report 22979 provides guidance on assessing the need for clinical investigations of IOL modifications (Table 2). However, the existing standards do not fully address issues regarding all premium IOLs. For new designs or products, the FDA recommends that manufacturers use the presubmission program, which is a mechanism to provide FDA feedback on nonclinical and clinical testing and for manufacturers to have an opportunity to meet with FDA staff to discuss new IOL designs.[5]

In the case of monofocal IOLs, the FDA-recognized ANSI/ISO standards provide detailed nonclinical and clinical recommendations. For monofocal IOL clinical investigations, best-corrected visual acuity is identified as the key effectiveness outcome measure, and AE rates are identified as the key safety outcome. The FDA's ability to communicate clear expectations for the initiation of a clinical trial under investigational device exemption (IDE) through recognition of these standards contributed to a 71% rate of full approval or approval with conditions after the initial "first round" of the IDE submission in fiscal years 2005 to 2013 for monofocal IOLs, based on internal data analyses.[6] In comparison, during the same time frame, only 39% of premium IOL IDEs were fully approved or approved with conditions within the first round of IDE submission. This differential approval rate, which can directly affect the time to the U.S. marketplace, can be partially attributed to the paucity of publicly available information on appropriate AE benchmarks and certain assessments specifically for investigational premium IOLs. Some of these assessments include validated methods for quantitating IOL tilt and decentration, reliably measuring accommodation, and measuring PROs. Development of AE benchmarks and assessments specifically for premium IOLs through discussions of expert stakeholders is an effective means to standardize review practices and expectations, while ensuring that premium IOLs for which reasonable assurance of safety and effectiveness has been demonstrated can efficiently gain marketing authorization through the premarket application process.

Table 1. Listing of Food and Drug Administration–Recognized Standards for Intraocular Lenses

Area Addressed	FDA-Recognized Standard
Preclinical requirements	ISO 11979 − 2, 3, 5, 6, 8 ANSI Z80 − 7, 12, 13
Clinical requirements	Monofocal IOL (ANSI Z80.7, ISO 11979-7) Multifocal IOL (ANSI Z80.12, ISO 11979-9) Phakic IOL (ANSI Z80.13, ISO 11979-10)
IOL modifications	ISO TR 22979

ANSI = American National Standards Institute; FDA = Food and Drug Administration; IOL = intraocular lens; ISO = International Organization for Standardization.

Centers for Medicare and Medicaid Services Intraocular Lens Payment Policies

Medicare pays fully for cataract surgery with conventional or monofocal IOLs. However, Medicare does not pay for refractive surgery and, in a similar fashion, does not pay for the astigmatic or presbyopia-correcting part of premium IOLs. Additional charges associated with the astigmatism-correcting or presbyopia-correcting aspect of cataract surgery with IOL implantation can be paid by the patient. Another Medicare policy governs new technology IOLs (NTIOLs), which are conventional IOLs with new features that meet certain regulatory requirements.[7] For a period of 5 years, IOLs with an NTIOL designation receive an additional payment of $50. According to Centers for Medicare and Medicaid Services regulation changes in 2013,[8] NTIOL designation requires FDA approval of the IOL and a label claim of a specific clinical benefit that results in an improved outcome in comparison with other existing conventional IOLs. An example of a past NTIOL designation that expired in 2012 was reduced spherical aberration IOLs, which had the benefits of improved night driving and contrast sensitivity under certain conditions. The NTIOL designation can come after the IOL is initially approved if further studies are performed to obtain the specific label claim necessary for this designation.

Premium Intraocular Lens Safety Assessments

A critical issue for the assessment of new premium IOLs is the limitation of the applicability of some of the current ANSI/ISO AE benchmarks to particular premium IOL types, because the historical rates (or "grid") from which these AE end points and targets were derived were developed in 1982 from pooled data of investigations of 17 different monofocal IOLs from 7 manufacturers (45 543 study cases and 8597 CORE cases).[9] In 1998, the FDA updated this grid using monofocal IOL data, and, in 2001,