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Incremental Revisions across the Life Span of Ophthalmic Devices after Initial Food and Drug Administration Premarket Approval, 1979–2015

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Purpose: To characterize the frequency, nature, and regulatory mechanisms by which ophthalmic devices are iteratively modified after initial Food and Drug Administration (FDA) Premarket Approval (PMA).

Design: Retrospective cross-sectional analysis using publicly available FDA data.

Participants: Ophthalmic devices initially approved via the FDA's PMA pathway between January 1, 1979 and December 31, 2015.

Methods: We used the FDA's PMA Database to identify and characterize initial approvals and subsequent postmarket modifications to Class III ophthalmic devices. The FDA Recalls Database was used to identify associated safety events.

Main Outcome Measures: Median iterated life span (timespan across which modifications occurred after initial PMA) and median number of supplements approved per device, by device type, and overall, stratified by regulatory pathway and modification type.

Results: Between 1979 and 2015, the FDA approved 168 original ophthalmic devices via the PMA pathway and 2813 subsequent modifications. More than one third (n = 64; 38%) of original approvals were intraocular lenses. Overall, devices underwent a median of 11 postmarket modifications (interquartile range [IQR], 3–24.8) across a median 10.0-year iterated life span (IQR, 4.1–16.7). The majority of devices (n = 144; 86%) underwent more than 1 postapproval modification, including more than 1 design modification (n = 84; 50%). The median number of changes altering device design or labeling was 3.5 (IQR, 1–9). Although manufacturing alterations (n = 834 of 2813; 30%) were the most frequent type of revision, changes involving device design (n = 667; 24%) and labeling (n = 417; 15%) were common. Recalled devices underwent more frequent postapproval modifications per year (median, 1.4; IQR, 0.7–2.3; mean, 1.5; 95% confidence interval, 1.1–1.9) in the period preceding recall than did nonrecalled devices (median, 0.5; IQR, 0.2–1.1; mean, 0.8; 95% confidence interval, 0.7–1.0) across their market approval period ($P < 0.001$).

Conclusions: Most ophthalmic devices approved via the FDA's PMA pathway have undergone extensive revisions, including serial design and labeling changes, since their initial approvals, often without supporting clinical data. Ophthalmologists should take into consideration that cumulative revisions may render the clinical evidence that supported an original FDA approval less relevant to newer device models. *Ophthalmology 2017;■:1–10* © *2017 by the American Academy of Ophthalmology*

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Medical devices used in the eye are subject to regulation by the U.S. Food and Drug Administration (FDA). Class III devices are those that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[1] Examples of such devices in ophthalmology include intraocular lenses (IOLs), excimer lasers, and certain intraocular pressure–reducing implants. Before commercialization, manufacturers of Class III devices must obtain approval via the FDA's Premarket Approval (PMA) pathway.[1] Unlike requirements for most Class II devices, which are often cleared on the basis of established equivalence to existing devices, approval of Class III devices via the PMA pathway generally requires the submission of clinical study data supporting the device's safety and effectiveness.[1,2] Despite this requirement, standards for initial approval of Class III devices have been generally criticized.[3–5] Among Class III ophthalmic devices, studies supporting initial PMA are of varying quality and rigor, raising concerns about their utility in predicting postapproval device performance.[6]

Understanding of device performance may be further complicated by postmarket modifications to devices, which often do not require new clinical evidence for approval.[7–10]

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Manufacturers of devices that have previously received PMA are not required in most cases to submit a new PMA application for proposed modifications; rather, manufacturers may submit "PMA supplements," which, although subject to the same regulatory standards as the initial PMA, may require different forms of evidence and rely on information previously submitted in earlier applications.[11,12] PMA supplements are designed to provide an efficient means for the FDA to review small-scale revisions to previously approved devices, which manufacturers may subsequently market as new models or under alternate trade names.[13] The FDA approves these changes via one of several PMA supplement review tracks (Table 1) on the basis of the type of change proposed, the level of review required, and supporting data requirements.[11,12] These review mechanisms are intended to maintain regulatory oversight of device changes while expediting the market availability of revised devices with potential benefits and limiting excess regulatory review.[7,13] Changes requiring submission of PMA supplements include alterations to device design, labeling, or manufacturing processes that may affect the device's safety and effectiveness.[11] The FDA often does not require new clinical data for these modifications, which are approved on the presumption that the clinical evidence demonstrating safety and effectiveness for the initial PMA remains valid even after the changes.[12]

Despite regulatory review, iterative postmarket device modifications can have significant clinical and public health impacts. Although minor changes may seem insignificant, the cumulative effect of incremental revisions compounded by the characteristic absence of clinical data evaluating their effects can result in marketed device models with safety and effectiveness profiles much different from their original PMAs, as illustrated by high-profile device failures within other specialties.[8,9,13] The literature contains several examples of unanticipated consequences resulting from incremental postmarket device modifications that were approved without supporting clinical data.[8,9,14] Among ophthalmic devices, Bausch & Lomb's (Rochester, NY) Hydroview IOL came under scrutiny in 1999, just before U.S. release, after addition of a silicone-sealing gasket to packaging resulted in development of capsulotomy-resistant lens opacifications in some patients that were ultimately linked to the silicone material used in the revised design.[15–18] Although this revision occurred outside the context of the PMA supplement process, the resulting adverse events implicated an incremental design modification in a significant global safety recall. In light of this, understanding the lineage of ophthalmic devices with potentially extensive postmarket changes is important for patients and clinicians, who may assume that newer device models represent safe, clinically proven innovations over precursors.[8,13,19]

Postmarket device modifications have not been characterized in the field of ophthalmology, despite heavy reliance on medical devices in patient care. We conducted a retrospective analysis of ophthalmic devices approved via the FDA's PMA pathway and their associated supplements with

Table 1. Food and Drug Administration Supplement Review Pathways for Postmarket Modifications to Premarket Approval Devices

Supplement Pathway	180-Day Supplement	Real-Time Supplement	Panel Track Supplement	Special Supplement†	30-Day Notice/ 135-Day Review§,‖
Year introduced	1986	1997	1990	1986	1997
Designated purpose*	Design	Design	Labeling	Labeling‡	Process
Types of changes	Major design changes, including new features, modifications to software or hardware, and new formulations	Minor design changes, typically anticipated for device class and within purview of single discipline	Labeling changes expanding indications of use or weakening contraindications	Safety-enhancing modifications, including stricter contraindications, warnings, and precautions, as well as instruction revisions	Manufacturing changes, including automation, new component or material suppliers, added testing procedures, and modified sterilization
Appropriate supporting evidence*	Preclinical data; limited clinical data in select instances	Preclinical data	Clinical data	None specified	Summary of validation studies or control procedures
Example	Addition of an iris identification system to an excimer laser	Creation of stand-alone component software derived from existing excimer laser system	Expanding procedural indication for excimer laser approved for photorefractive keratectomy to include LASIK	Improved instructions for operation of excimer laser system	New polymethylmethacrylate supplier for single-piece IOL production

FDA = Food and Drug Administration; IOL = intraocular lens; PMA = Premarket Approval.
*As recommended in FDA industry guidance documents.
†May be enacted before FDA approval of change.
‡Special supplements may be used for approval of certain safety-enhancing manufacturing changes, such as addition of quality-control measures.
§Certain changes may be reported to the FDA via a 30-day supplement, which is not the same as a 30-day notice; this alternative pathway is used on a case-by-case basis for changes determined by the FDA as not requiring PMA supplement submission.
‖Initial 30-day notices may be upgraded to 135-day reviews if the FDA deems initially submitted information inadequate.

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