Postmarket Modifications of High-Risk Therapeutic Devices in Otolaryngology Cleared by the US Food and Drug Administration

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective: The US Food and Drug Administration (FDA) grants initial marketing clearance for novel high-risk medical devices via the premarket approval (PMA) pathway, which requires clinical data demonstrating safety and effectiveness. Manufacturers may subsequently file supplemental PMA applications (supplements) to implement incremental device changes, usually without additional clinical data. Given the potentially significant clinical implications of using new device models, this study characterized the frequency and nature of changes to high-risk therapeutic otolaryngic devices cleared via the PMA pathway.

Study Design: Retrospective cohort study.

Setting: FDA PMA database.

Methods: Original high-risk therapeutic otolaryngic devices and supplements were identified. Supplements were characterized by clearance date, change type, and review track, including real-time (design-minor) and 180-day (design-major) tracks. Median device lineage life span (postmarket period over which changes occurred) and median number of changes per original device were calculated.

Results: Through 2014, the FDA cleared 14 original high-risk therapeutic otolaryngic devices via the PMA pathway and 528 incremental changes via supplements. Devices were modified over a median 10.5-year life span (interquartile range, 4.4-15.8; range, 0.7-24.1), and they underwent a median 22 changes (interquartile range, 10-70; range, 2-108). Over half (272 of 528; 52%) altered device design, most of which were reviewed via the 180-day track (199 of 272; 73%) intended for major design changes. Few real-time design changes (11 of 73; 15%) were designated by the FDA as “minor.”

Conclusion: A substantial number of incremental changes have been made to high-risk therapeutic otolaryngic devices over time, including many major design changes without supporting clinical data.

Keywords

otolaryngology, medical device, premarket approval, postmarket

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In the United States, manufacturers must receive marketing clearance from the US Food and Drug Administration (FDA) prior to commercializing high-risk medical devices. High-risk (ie, FDA class III) medical devices are defined as those that support or sustain human life, are of substantial importance in preventing illness, or present potential unreasonable risk to patients. Since passage of the 1976 Medical Device Amendments Act, the FDA has granted marketing clearance for novel high-risk medical devices through the premarket approval (PMA) regulatory pathway.1 The PMA pathway is the most rigorous route to market, as manufacturers are required to provide premarket clinical study data demonstrating medical device safety and effectiveness, and must submit supplemental applications for FDA review whenever postmarket changes affecting device safety and effectiveness are made. Among others, these changes include major and
minor modifications to device labeling, design, and production processes. The PMA supplement pathway is intended to serve as an efficient and inexpensive means for patients to benefit from incremental changes to devices as they are developed and for manufacturers to ensure compliance with FDA requirements as their production processes evolve.

In an effort to facilitate patient access to therapeutic innovations, Congress has mandated that the FDA require manufacturers to provide only “the least burdensome” data necessary for review. As a result, FDA regulation of medical devices has drawn much criticism in recent years. In the postmarket period, there are concerns that high-risk devices may often undergo extensive modifications via the PMA supplement pathway without supporting clinical evidence. In a recent study, implantable cardiac electronic devices were found to have accumulated nearly 30 labeling or design changes over their market lives via the PMA supplement pathway, with approximately one-fifth of major design changes supported by new clinical data. After receiving FDA clearance for major design changes, manufacturers may modify existing devices and market them as new products, such as the best-selling and recently recalled Cochlear Nucleus CI500. Patients and physicians may assume that iteratively developed device models are safe and proven advancements over previous versions, as these technologies are rapidly incorporated into clinical practice following FDA clearance. However, it is unclear how much public awareness there is that the regulatory process for iterative device design usually does not require new clinical evidence. The decision to adopt new device models merits careful consideration; devices are often implanted in patients, with a high cost of failure. For instance, the Advanced Bionics CII cochlear implant was recalled from the market after cases of otogenic meningitis were linked to the addition of an electrode positioner, a design change that was cleared via the PMA supplement pathway. Given the potentially significant clinical implications of adopting new device models, the objective of this study was to characterize the nature and frequency of incremental changes made to high-risk therapeutic otolaryngic devices via the PMA supplement pathway.

**Methods**

**Study Sample**

A sample of all high-risk therapeutic otolaryngic devices receiving US marketing clearance via the FDA PMA pathway was constructed using the publicly accessible PMA database, which contains summary information on all initial and supplemental PMA applications cleared through December 31, 2014. The original version of a novel high-risk device is cleared for marketing via an initial PMA application, whereas incremental changes to the original version are cleared via successive supplemental PMA applications (ie, supplements); the PMA database links each original device version with all of its subsequently cleared incremental changes to create a lineage of device iterations. To identify otolaryngic devices, the database was queried on January 11, 2015 for all initial PMA applications and ensuing supplements assigned to the FDA Ear, Nose, and Throat Devices Panel. Information on device type listed within the database was used to exclude nontherapeutic (ie, diagnostic) devices, all of which were endoscopic imaging systems.

**PMA Supplement Pathway Review Tracks**

The PMA supplement pathway has 6 review tracks (Table I). Each review track is intended to examine a specific class of proposed changes, has unique supporting data requirements, and is subject to different review times and user fees. Manufacturers seeking to alter the labeling, design, or production process of an existing device must determine the review track that best corresponds to the proposed change. However, the FDA may require that an alternative review track be used for a proposed change if necessary.

Special (immediate) track and panel track supplements are primarily intended to review changes in device labeling. Panel track supplements are the most stringently reviewed changes; these supplements are suggested for labeling changes that expand indications for use or weaken/remove contraindications, and generally require a new supporting clinical study for clearance. In contrast, special (immediate) track supplements are allowed for labeling changes that enhance device safety and require no specific supporting data.

Real-time and 180-day track supplements are primarily intended to review changes in design that affect device safety and effectiveness. The 180-day track supplements are suggested for significant design changes and require supporting preclinical data (eg, mechanical testing) for clearance; the FDA may additionally stipulate that manufacturers provide limited clinical data demonstrating the expected performance of a device iteration. In contrast, real-time supplements are intended to review “minor” design changes and require only supporting preclinical data.

The 30-day notice and 135-day supplements are intended to review changes in production processes that affect device safety and effectiveness. The 30-day notice supplements allow manufacturers to commercially distribute devices produced under a modified protocol 30 days after giving the FDA written notice, provided that the FDA does not specify otherwise. Manufacturers must supply the FDA with “adequate” information describing and validating the change to receive clearance, or else the FDA may require additional supporting information and convert the 30-day notice to a 135-day supplement.

**Data Abstraction**

The following information was collected from the PMA database to characterize each original high-risk therapeutic otolaryngic device and lineage of subsequent device
iterations: initial clearance date, device type, implantable status (yes/no), manufacturer, and number of incremental changes (ie, supplements). Device type and implantable status were determined using FDA-designated product classification codes. In addition, device lineage recall history was characterized by searching the FDA’s Medical Device Recalls Database for each PMA application number and recording any resulting recall dates; this online database contains all recalls issued since November 1, 2002.

Through the PMA database, each incremental change was characterized by abstracting the clearance date, supplement review track (as described previously), and type of change cleared. In examining the type of change cleared via each review track, only labeling, design, and production process changes were included; all other changes (eg, new manufacturing locations) were excluded from analysis. Changes were categorized based on the FDA-designated reason given for each supplement (Table 2).

**Data Analysis**

Descriptive statistics were used to characterize the features of original high-risk therapeutic otolaryngic devices. The median number of incremental changes per original device and the median duration of device lineage life span were then calculated. The duration of device lineage life span was calculated by subtracting the initial PMA application clearance date from the most recent supplement clearance date.

Next, trends in the use of supplements over time were analyzed. The total number of supplements cleared per active device lineage was calculated and differentiated by review track for each year between 1990 and 2014; a device lineage was considered to be active in years within its life span. The total number of supplements was divided by the number of active device lineages in each year to account for the introduction and removal of device lineages from the market. Finally, descriptive statistics were used to characterize the types of incremental changes cleared via each supplement review track.

**Results**

The FDA has cleared 14 original high-risk therapeutic otolaryngic devices via the PMA pathway, each of which served as the basis for a lineage of device iterations (Table 3). Half (n = 7; 50%) were initially cleared between 2000 and 2014. All were implantable (n = 14; 100%). The majority were otologic (n = 12; 86%), and more than half (n = 8; 57%) were cochlear implants; the top 3 cochlear implant manufacturers (Cochlear, MED-EL, and Advanced Bionics) accounted for more than two-thirds (n = 10; 71%) of original devices, with Cochlear accounting for nearly half (n = 6; 43%). Following initial FDA clearance, 3 (21%) device lineages underwent at least 1 recall (Figure 1).

The FDA cleared 528 total incremental changes to these 14 original devices through December 31, 2014. Whereas 23 (4%) changes were reviewed as special (immediate) track supplements for safety-enhancing modifications, only 1 (0.2%) was reviewed as a panel track supplement with supporting clinical evidence to expand indications for use. Half (n = 264; 50%) of all changes were reviewed as...
180-day track supplements, which have been primarily intended for significant design changes since 1997. In contrast, less than one-fifth (n = 98; 19%) were reviewed as real-time process supplements, which are allowed for minor design changes. The FDA cleared 138 (26%) changes related to production processes: the majority (n = 99 of 138; 72%) were cleared through 30-day notice supplements, although the FDA required additional information from manufacturers for review via 135-day supplements for approximately one-quarter (n = 39 of 138; 28%).

### Device Lineage Life Span

The median life span over which high-risk therapeutic otorhinolaryngic devices were iteratively modified was 10.5 years (interquartile range [IQR], 4.4-15.8; range, 0.7-24.1; **Figure 1**), with devices undergoing a median of 22 incremental changes (IQR, 10-70; range, 2-108). Excluding production process changes implemented via 30-day notice and 135-day supplements, devices underwent a median of 14 incremental changes (IQR, 7-51; range, 2-83) over their life spans.

Prior to March 2014, the most recent original PMA application for any cochlear implant was cleared in August 2001. In early 2014, all cochlear implants available on the US market were therefore iterations of devices originally cleared over a decade earlier. For instance, the MED-EL Combi 40+ cochlear implant underwent 72 incremental changes via the PMA supplement pathway over this period (real-time: 16 [22%], 180-day track: 23 [32%]) after receiving initial clearance in 2001. In 2003, the Combi 40+ was cleared for marketing as the first magnetic resonance imaging–safe cochlear implant through a 180-day track

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### Table 2. Categorization by Type for Incremental Changes to High-Risk Medical Devices Cleared via the FDA Premarket Approval Supplement Pathway.

<table>
<thead>
<tr>
<th>Incremental Change Type</th>
<th>FDA-Designated Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labeling</td>
<td>“Labeling Change—Instructions”</td>
</tr>
<tr>
<td>Labeling—Instructions</td>
<td>“Labeling Change—Indications”</td>
</tr>
<tr>
<td>Labeling—All Other</td>
<td>“Labeling Change—Minor”</td>
</tr>
<tr>
<td></td>
<td>“Labeling Change—Shelf Life”</td>
</tr>
<tr>
<td></td>
<td>“Labeling Change—Trade Name”</td>
</tr>
<tr>
<td></td>
<td>“Labeling Change—Other”</td>
</tr>
<tr>
<td>Design</td>
<td>“Design Change—Minor”</td>
</tr>
<tr>
<td>Design—Component</td>
<td>“Change Design / Components / Specifications—Component”</td>
</tr>
<tr>
<td></td>
<td>“Change Design / Components / Specifications—Software”</td>
</tr>
<tr>
<td></td>
<td>“Change Design / Components / Specifications—Specifications”</td>
</tr>
<tr>
<td>Design—All Other</td>
<td>“Change Design / Components / Specifications—Other”</td>
</tr>
<tr>
<td>Production</td>
<td>“Process Change: Manufacturing”</td>
</tr>
<tr>
<td>Production—Manufacturing</td>
<td>“Process Change: Packaging”</td>
</tr>
<tr>
<td>Production—All Other</td>
<td>“Process Change: Sterilization”</td>
</tr>
<tr>
<td></td>
<td>“Process Change—Other”</td>
</tr>
</tbody>
</table>

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### Table 3. Original High-Risk Therapeutic Otolaryngic Devices Cleared via the FDA Premarket Approval Pathway.

<table>
<thead>
<tr>
<th>Devices (n = 14)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial clearance date</td>
<td></td>
</tr>
<tr>
<td>1980-1989</td>
<td>2 (14)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>5 (36)</td>
</tr>
<tr>
<td>2000-2009</td>
<td>4 (29)</td>
</tr>
<tr>
<td>2010-present</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Implantable</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (100)</td>
</tr>
<tr>
<td>No</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Device type</td>
<td></td>
</tr>
<tr>
<td>Cochlear implant</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Middle ear hearing implant</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Auditory brainstem implant</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Drug-eluting sinus stent</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Upper extremity neural prosthetic</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
</tr>
<tr>
<td>Cochlear</td>
<td>6 (43)</td>
</tr>
<tr>
<td>MED-EL</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Advanced Bionics</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (29)</td>
</tr>
</tbody>
</table>

Abbreviation: FDA, US Food and Drug Administration.

*Percentages may not sum to 100% due to rounding.
supplement, although the meaning of such labeling has been called into question in the context of adverse events such as severe pain and magnet dislocation.

**Supplement Trends**

The median number of supplements cleared per year tripled between the 1990s (n = 12) and 2010 onward (n = 36); however, the number of supplements cleared per active device lineage per year did not appear to increase between 1990 and 2014 (Figure 2), as the number of active device lineages increased overall during this period (data not shown). Beginning in 1998, the FDA began clearing changes previously reviewed via 180-day supplements through real-time, 30-day notice, and 135-day supplements. Between 1998 and 2014, a median 4 supplements (IQR, 2-5; range, 1-7) were cleared per active device lineage per year. Excluding production process changes implemented via 30-day notice and 135-day supplements, a median 2 supplements (IQR, 1-3; range, 1-5) were cleared per active device lineage per year over this period. In 2007, the FDA issued comprehensive guidance for manufacturers on the intended use of each supplement review track; the annual number of 30-day notice and 135-day supplements (ie, production process changes) cleared per active device lineage subsequently increased, while the corresponding number of real-time and 180-day track supplements (ie, design changes) decreased thereafter.

**Changes by Supplement Review Track**

As recommended by FDA guidance, virtually all special (immediate) track (n = 22 of 23; 96%) and panel track (n = 1 of 1; 100%) supplements were submitted for review of labeling changes, and all 30-day notice (n = 99 of 99; 100%) and 135-day (n = 39 of 39; 100%) supplements were for production process changes (Figure 3). Similarly, all design changes (total n = 272) were reviewed either via real-time (n = 73; 27%) or 180-day track (n = 199; 73%) supplements. However, the FDA designated a small fraction of real-time design changes (n = 11; 15%) as “minor” in nature, with the remainder designated as component (n = 37; 51%), material/software/specifications (n = 16; 22%), or other (n = 9; 12%) design changes. Of note, a real-time labeling change in indications was identified, although FDA guidance prohibits such use of the real-time review track.
in this case, the new indications no longer specified the device as second-line treatment. In addition, 4 instances were identified in which labeling changes expanding indications for use were cleared via 180-day track supplements, although such changes are intended to undergo more stringent review via panel track supplements.

**Discussion**

In this study of the FDA PMA supplement pathway, high-risk therapeutic otolaryngic devices were found to undergo a median of 22 incremental changes via supplements over a median 10.5-year postmarket life span. Just over half of all incremental changes altered device design, and nearly three-quarters of design changes were reviewed via 180-day track supplements as “significant” modifications affecting device safety and effectiveness. Although real-time supplements are intended to review more “minor” modifications and require fewer supporting data, the FDA designated only 15% of all real-time design changes as “minor.” Of note, several instances were identified in which labeling changes expanding indications for use were cleared via real-time and 180-day track supplements; FDA guidance recommends that manufacturers submit panel track supplements with substantial supporting clinical data for review of changes in indication.

Given the significant clinical implications of device failure, otolaryngologists should understand that new device models are generally marketed without supporting clinical evidence, and the accumulation of incremental changes over time may lead devices used in practice to differ substantially from those originally described in published studies. Expansion of current FDA outreach efforts through social media and other consumer-facing websites (eg, Wikipedia) could help keep otolaryngologists and their patients digitally updated on clinically significant device changes. Although manufacturers are required to provide information on the cumulative effects of incremental changes as part of PMA supplement applications, this information is not presently accessible to inform clinical practice. In recent years, the FDA has begun to release review memos outlining the supporting data for major design changes implemented via 180-day track supplements in an effort to improve transparency; more than 200 memos have been released since 2010. However, no memos pertaining to otolaryngic devices have been made publicly available to facilitate the evidence-based adoption of new models.

While it is important that otolaryngologists understand the premarket evidence for new device models, there is now an increased emphasis on postmarket assessment of their clinical performance. To address clinical questions during the postmarket period (eg, about long-term device performance), the FDA may require manufacturers to conduct additional studies as a condition of approval for devices cleared via the PMA pathway; half of all device lineages cleared since 1995 have been subject to at least 1 such postapproval study. To date, the FDA has required only 2 postapproval studies for 1 new high-risk therapeutic otolaryngic device iteration, both of which enrolled <100 patients and were completed over 5 years ago. In fields such as cardiology, orthopedics, and plastic surgery, professional societies, hospitals, and manufacturers have established much larger patient registry studies with the aim of providing real-world information on longitudinal outcomes and comparative effectiveness of devices. Recently, several large international registries have been initiated to follow cochlear implant patients and the potential to improve US public health through similarly coordinated postmarket surveillance of high-risk therapeutic otolaryngic devices deserves careful consideration.

This study is the first to characterize the regulation of medical devices within the field of otolaryngology. Prior work examining regulation of high-risk medical devices via the FDA PMA pathway has largely centered on the premarket evaluation of technologies, with emphasis on cardiovascular devices. The findings of this study were comparable with those of the other study investigating PMA...
supplements, which focused on implantable cardiac electronic devices; a similar duration of device iteration life span and yearly number of supplements per device lineage were observed. While the previous study reported an overall higher number of supplements per device lineage, this difference was predominantly due to production process supplements. In contrast, a higher proportion of design changes was observed for otolaryngic devices as compared to cardiac devices (52% vs 37%), and the proportion of design changes reviewed via 180-day track supplements was much higher among otolaryngic devices (73% vs 32%). Although preceding literature on the uncertain clinical performance of higher among otolaryngic devices (73% vs 32%), and the proportion of design was observed for otolaryngic devices as compared to cardiac devices (52% vs 37%), and the proportion of design changes reviewed via 180-day track supplements was much higher among otolaryngic devices (73% vs 32%). Although preceding literature on the uncertain clinical performance of new device models has primarily featured cardiovascular and orthopedic technologies, this study demonstrates the need for such perspective in the field of otolaryngology and offers additional granularity in characterizing the nature of incremental changes cleared through each supplement review track.

Although this study offers a novel perspective on regulatory science within otolaryngology, there are several limitations merit discussion. This study relied on the PMA database, which contains limited information on the nature of changes implemented via supplements. It is therefore difficult to determine whether significant device changes (ie, major design modifications and expanded indications) reviewed via less rigorous supplements than intended by the FDA were cleared on the basis of inadequate evidence. Additional information clarifying the specific details and supporting evidence for these changes is needed to give such apparent discrepancies proper clinical context. Of note, this study did not include all high-risk therapeutic otolaryngic devices, as 1 device was cleared prior to establishment of the PMA pathway under the 1976 Medical Device Amendments Act. In addition, this study was limited to high-risk devices and did not include a number of important moderate-risk devices in otolaryngology (eg, tympanostomy tubes) which are regulated through the separate, less stringent 510(k) pathway. PMA devices are subject to the most stringent evidentiary requirements, and it is likely that moderate-risk otolaryngic devices are both initially cleared for marketing and subsequently iterated with fewer supporting clinical data. Finally, this analysis represents a snapshot in time, and it is certain that the duration of device iteration life span and number of incremental changes to each device reported herein will become underestimates, as many device lineages continue to undergo modification.

Given that future high-risk device iterations will further diverge from the original versions described in the literature, otolaryngologists should be aware that devices may undergo substantial modification over time through a regulatory process that rarely requires clinical evidence. As a result, familiarity with a specific device model may not guarantee its future performance, and new models may be marketed without identifiable supporting clinical evidence. Establishing coordinated postmarket surveillance within otolaryngology may help address such gaps in clinical evidence while allowing patients to benefit from incremental innovation in devices.

Author Contributions
Vinay K. Rathi, study conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising manuscript critically for important intellectual content, final approval; Joseph S. Ross, study conception and design, analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval; Andre M. Samuel, analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval; Saral Mehra, study conception and design, analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval.

Disclosures
Competing interests: Joseph S. Ross, receives research support through Yale University from Medtronic, Inc and Johnson & Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services to develop and maintain performance measures that are used for public reporting, and from the US Food and Drug Administration to develop methods for postmarket surveillance of medical devices; is also supported by the National Institute on Aging (K08 AG032886) and by the American Federation for Aging Research through the Paul B. Beeson Career Development Award Program.

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