Device Safety

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KEYWORDS

- Medical device
- Otolaryngology
- FDA
- Premarket approval
- 510(k)
- Postmarket studies

KEY POINTS

- The type and strength of premarket evidence required by the US Food and Drug Administration (FDA) for device clearance or approval predominantly depends on device risk classification (low-risk, moderate-risk, or high-risk).
- Moderate-risk devices (eg, vocal fold injectables and ossicular prostheses) are cleared for marketing via the 51(k) pathway and typically do not require premarket clinical evidence of safety.
- High-risk devices (eg, cochlear implants and dermal fillers) are approved for marketing via the premarket approval pathway and require premarket clinical evidence providing reasonable assurance of safety and effectiveness.
- The FDA conducts both passive (adverse event reporting) and active (manufacturer-required studies) postmarket surveillance to address important safety questions (eg, long-term outcomes or rare adverse events).
- The FDA is currently developing advanced methods of postmarket surveillance that leverage clinically based data sources, which may include the society-sponsored otolaryngology registry in the future.

INTRODUCTION

Medical devices are essential in the diagnosis and treatment of otolaryngologic disease. The US Food and Drug Administration (FDA) is tasked with assuring the safety and effectiveness of these devices. Otolaryngologists, in turn, are often responsible for helping patients to understand risks, benefits, and alternatives when deciding whether a device should be used in their medical care. To best counsel patients, otolaryngologists should be aware of the strengths and limitations of device regulation by the FDA. This article provides an overview of the FDA regulatory framework for medical devices.
medical devices, premarket safety standards for marketing devices, and postmarket methods of safety surveillance. Future directions for monitoring device safety are reviewed as well.

US FOOD AND DRUG ADMINISTRATION REGULATORY FRAMEWORK

The Medical Device Amendments of 1976 first established a 3-tiered risk classification system for the regulation of medical devices.1 Under this statute, the FDA categorizes devices into 1 of 3 classes (class I—low risk, class II—moderate risk, and class III—high-risk) (Table 1) based on the level of control necessary to assure safety and effectiveness.2 These controls include general controls, special controls, and premarket approval (PMA) or humanitarian device exemption (HDE)3:

- General controls—basic provisions, such as good manufacturing practices, lawful labeling, and manufacturer registration with the FDA
- Special controls—device-specific controls necessary to assure safety and effectiveness, such as performance standards or special labeling requirements
- PMA/HDE—regulatory pathways requiring premarket clinical evidence of safety and effectiveness (PMA) or probable benefit (HDE)

**Low-Risk (Class I) Devices**

Approximately two-thirds of all medical devices are classified as low-risk.4 These devices, with few exceptions, are subject only to general controls and do not undergo premarket review by the FDA. Otolaryngologic examples include devices, such as tongue depressors and otoscopes.

**Moderate-Risk (Class II) Devices**

Approximately one-third of devices are classified as moderate-risk.4 These devices are subject to both general controls and special controls. To market moderate-risk devices, manufacturers must obtain FDA clearance via the 510(k) process.5 Otolaryngologic examples include devices, such as ossicular prostheses and vocal fold implants.

**High-Risk (Class III) Devices**

Few (1%–2%) devices are classified as high-risk.4 High-risk devices are defined as those that (1) support or sustain life, (2) are of substantial importance in preventing illness, or (3) present potentially unreasonable risk to patients.6 High-risk devices are predominantly approved via the PMA pathway, which is the most rigorous method of FDA premarket review. For high-risk devices intended to diagnose or treat rare (affecting <8000 US patients per year) diseases, manufacturers may seek marketing authorization through the less rigorous HDE pathway7; no otolaryngologic devices have been approved via the HDE pathway to date.8 Examples of high-risk devices include cochlear implants and dermal fillers.

PREMARKET SAFETY STANDARDS

The type (ie, nonclinical or clinical) and strength of premarket evidence required by the FDA predominantly depends on device risk classification. By law, the FDA may only compel manufacturers to provide the minimum amount of information necessary to assure safety and effectiveness.9 As a result, low-risk and moderate-risk devices are typically cleared without supporting clinical evidence,4,10,11 and high-risk devices are often approved on the basis of limited clinical studies.12–15 Although this approach is intended to facilitate patient access to innovative technologies and is more stringent
<table>
<thead>
<tr>
<th>Device Class</th>
<th>Risk</th>
<th>Examples</th>
<th>Proportion&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Regulatory Controls</th>
<th>Review Pathway</th>
<th>Review Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Low-risk</td>
<td>Tongue depressor, Otoscope</td>
<td>67%</td>
<td>General controls</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Class II</td>
<td>Moderate-risk</td>
<td>Ossicular prosthesis, Vocal fold injection</td>
<td>31%</td>
<td>General controls and special controls (device-specific)</td>
<td>510(k) process&lt;sup&gt;c&lt;/sup&gt;</td>
<td>“Substantial equivalence” to predicate device&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class III</td>
<td>High-risk</td>
<td>Cochlear implant, Dermal filler</td>
<td>1%</td>
<td>General controls and PMA</td>
<td>PMA</td>
<td>Clinical evidence of safety and effectiveness</td>
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<td>&lt;1%</td>
<td>General controls and HDE</td>
<td>HDE&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Clinical evidence of safety and “probable benefit”</td>
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<sup>a</sup> Source: Institute of Medicine. Medical devices and the public’s health: the FDA 510(k) clearance process at 35 years. 2011.
<sup>b</sup> Exceptions include select class I devices subject to 510(k) review.
<sup>c</sup> Exceptions include select class II devices exempt from 510(k) review.
<sup>d</sup> Exceptions include class I and class II devices without predicates subject to de novo review.
<sup>e</sup> Reserved for select class III devices indicated for the diagnosis or treatment of uncommon illnesses.

than European policy, the FDA nonetheless has come under scrutiny in recent years after a series of high-profile recalls of unsafe devices, such as metal-on-metal hip replacement prostheses, pelvic mesh implants, and implantable cardioverter-defibrillators.

**510(k) Process**

The 510(k) process requires manufacturers to demonstrate that a new or modified device is “substantially equivalent” to a previously cleared “predicate device” with respect to intended use and technological characteristics. The FDA generally grants clearance on the basis of nonclinical evidence, such as bench testing and technical specifications. Clinical evidence of safety and effectiveness is rarely required to validate substantial equivalence; just one-quarter of recently cleared otolaryngologic devices were supported by premarket clinical testing, which largely comprise small, uncontrolled studies.

The 510(k) process has earned much criticism in the wake of recent public health crises related to faulty devices. Debate over the 510(k) process has centered around 6 key issues:

1. **Split predicates**—manufacturers were historically permitted to market entirely novel devices on the basis of substantial equivalence to a combination of features derived from predicates with different intended uses and technological characteristics. For instance, the FDA cleared the first sinus balloon device in 2005 as an amalgam of a lacrimal dilator, a circular cutting punch, and an antrum curette.

2. **High-risk device exemptions**—until recently, the FDA has allowed manufacturers to market certain high-risk devices, such as mandibular reconstruction plates, via the 510(k) process. These devices were initially granted temporary exemption from more rigorous premarket review as a transitional measure under the Medical Device Amendments of 1976.

3. **Unsafe predicates**—manufacturers may obtain clearance on the basis of substantial equivalence to unsafe predicates, including permanently recalled devices. Few otolaryngologic devices cleared via the 510(k) process have been subject to FDA recall and none has been recalled for life-threatening or serious health hazards to date.

4. **Dissimilar predicates**—permissive regulation has enabled manufacturers to obtain clearance for unproved new devices based on substantial equivalence to predicates with different intended uses and technological characteristics.

5. **Predicate creep**—iterative device modification and application of substantial equivalence can result in the clearance of unproved new devices that differ substantially from better characterized predicates. For example, a calcium hydroxyapatite–based vocal fold implant was recently cleared without specific supporting clinical evidence. Clearance was based on a lineage of predicate devices originating in 1985 with a bovine bone graft indicated for dental and oromaxillofacial reconstruction. Modified versions of existing devices (eg, design alterations or labeling updates in intended use) account for approximately half of all 510(k) clearances.

6. **Lack of transparency**—premarket scientific data supporting FDA clearance of new devices are rarely accessible to help inform decision making by patients and physicians. In a recent study, performance data were not publicly available within FDA clearance summaries for more than 80% of otolaryngologic devices.

Although most devices recalled for life-threatening or serious health hazards are marketed with 510(k) clearance, patients and physicians may have few legal options,
because the US Supreme Court has ruled that substantial equivalence is not a determination of safety and effectiveness and manufacturers are exempt from tort litigation over device defects.26,27 Given weaknesses of the system and lack of recourse against manufacturers, the National Academy of Medicine recommended that the FDA replace the 510(k) process with an entirely new regulatory framework for moderate-risk devices in 2011,4 a directive that the agency is now seriously considering.28 In the interim, the FDA has taken several steps to strengthen the 510(k) process, such as banning split predicates, prohibiting review of high-risk devices,24 and increasing the public availability of scientific data.29

Premarket Approval

The PMA pathway requires manufacturers to submit clinical evidence providing reasonable assurance of safety and effectiveness to market new high-risk devices.6 Manufacturers generate initial safety data through in vitro (phase I) and feasibility (phase II) studies, which may offer important insights to guide premarket development (eg, design modifications) and clinical use (eg, anatomic restrictions) and inform the design of pivotal (phase III) studies.30 FDA premarket review of high-risk devices primarily centers on pivotal study results.31

In contrast to the United States, the European Union requires manufacturers only to demonstrate that high-risk devices perform “as intended” and are likely safe.17 Although this less stringent approach facilitates earlier patient access to new technologies, devices first approved in the European Union are more likely to be subject to postmarket safety alerts and recalls.16 Furthermore, no high-risk otolaryngologic devices have been recalled for life-threatening or serious health hazards to date.15 Nonetheless, recent work has highlighted several important limitations in the premarket clinical evidence supporting FDA approval of high-risk devices:

1. Strength of evidence—unlike prescription drugs, which are typically approved on the basis of 2 randomized double-blind controlled trials,32 high-risk devices are most often approved on the basis of a single pivotal clinical study without blinding, comparators, or clinical endpoints.12–15 In addition, pivotal study follow-up is often limited in duration, despite the fact that many high-risk devices are designed for long-term implantation. Among implantable high-risk otolaryngologic devices, the median pivotal study follow-up was approximately 26 weeks.15

2. External validity—compared with drug trials, pivotal studies of devices are small33; enrollment is generally less than 120 patients for high-risk otolaryngologic devices.15 Moreover, important patient groups, including women, children, the elderly, and minorities, are under-represented in pivotal studies.34 To address this issue, the FDA has recently implemented initiatives to diversify enrollment and better understand device performance in these patients.35

3. Device modifications—after initial approval, manufacturers must submit supplemental applications to implement labeling, design, and manufacturing changes that have an impact on device safety and effectiveness.36 Clinical data are typically required only for supplemental applications expanding device indications for use (eg, to include new patient populations).37,38 Devices may undergo substantial postmarket modification via supplemental applications37,39; high-risk otolaryngologic devices often undergo more than 20 such changes.38 Although supplemental applications may facilitate rapid iterative improvement in device performance, these modifications may also result in new versions that differ from the models originally evaluated in pivotal studies or result in unintended clinical consequences.38,40–42
POSTMARKET SAFETY SURVEILLANCE

Given constraints of premarket evaluation, the FDA has adopted a total product life-cycle approach to medical device regulation. This approach enables the FDA to address uncertainties about device risks and benefits that are present at the time of approval or arise in the context of real-world use. This includes questions about long-term safety, rare adverse events, or new indications. The FDA presently conducts both passive (ie, adverse event reporting) and active (ie, required clinical studies) postmarket surveillance, although both mechanisms have important limitations. The agency is also developing new methods to identify problematic devices and characterize product performance using clinically based data sources, such as claims, registries, and electronic health records.

Adverse Event Reporting

The FDA conducts passive postmarket surveillance by monitoring adverse event reports submitted by manufacturers, health care facilities, and providers. All manufacturers and health care facilities (eg, hospitals) are required to report all deaths and serious adverse events attributable to known or suspected device malfunction. In addition, the FDA has partnered with several hundred clinical sites (known as the Medical Product Safety Network) to collect complementary safety data (eg, close calls) and perform targeted surveillance. Although providers and patients are not mandated to report adverse device events, the FDA MedWatch program enables voluntary electronic reporting of adverse events. Patients, providers, and other interested parties (eg, researchers) may access adverse event reports through a publicly available online FDA database. Although such reports may prove valuable in identifying safety concerns, the FDA and others have noted that the utility of passive postmarket surveillance may be limited by several important factors:

1. Reporting quality—adverse event reports are not standardized and may be submitted by individuals unfamiliar with the details of clinical care. As a result, reports often include insufficient information to identify devices and characterize adverse events. Prior work in the field of otolaryngology has demonstrated that variable report quality may preclude meaningful systematic analysis of adverse device events.

2. Under-reporting—many adverse events are never reported as a result of poor end-user engagement; less than 10% of adverse event reports are submitted by patients or providers, who may fail to identify potentially problematic devices, fear legal repercussions, or lack the capability to integrate reporting into clinical operations.

3. Delayed/biased reporting—manufacturers decide whether adverse events are due to device malfunctions and need not report complications deemed unrelated. This may lead manufacturers to attribute events to other factors (eg, procedural error), minimize the severity of negative outcomes, or significantly delay reporting. Furthermore, reporting by patients and providers may be biased by extraneous factors (eg, media coverage).

4. Lack of denominator—prior to initial implementation of unique device identifiers by the FDA in 2014, there was no way to ascertain the total number of devices in clinical use. Along with under-reporting, this limitation precludes calculation of productspecific adverse event rates and hinders the detection of safety concerns.

Despite current limitations of passive postmarket surveillance, adverse event reporting via MedWatch allows patients and clinicians to provide the FDA with real-
world insights into device safety without fear of retribution. Given that federal certification criteria now require electronic health records to capture unique device identifiers for implantable technologies, many providers may soon be enabled to contribute to surveillance efforts in the course of clinical practice.

Postmarket Studies

The FDA conducts active postmarket surveillance by requiring device manufacturers to conduct additional studies after initial clearance or approval. Depending on device risk classification and the question to be addressed, the FDA may order 2 types of postmarket studies:

1. 522 Postmarket Surveillance Studies (522 Studies)—these studies are typically initiated in response to safety concerns arising in the context of real-world use and may be ordered for up to 3 years in duration for both moderate-risk and high-risk devices that meet any of the following 4 criteria:
   a. Failure likely resulting in serious adverse health consequences
   b. Expected significant use in pediatric populations
   c. Intended for implantation in the body for over a year
   d. Intended to be a life-sustaining or life-supporting device

   The FDA has ordered approximately 400 522 Studies to date. Nearly all have examined moderate-risk devices cleared via the 510(k) pathway, with more than three-quarters examining metal-on-metal hip implants or pelvic meshes. Only one 522 Study has been initiated to evaluate an otolaryngologic device, a tympanostomy tube cleared for placement in pediatric patients under sedation; this ongoing study was ordered in 2016 to assess the rate and risk factors for conversion to general anesthesia and has thus far progressed inadequately according to the FDA.

   The potential for 522 Studies to inform FDA regulation and clinical practice has often been limited by significant delays in completion, which may occur as a result of insufficient enrollment, manufacturer incentives to minimize safety concerns, and difficulties finalizing research protocols (eg, due to disagreements between the FDA and manufacturers); nonetheless, the FDA rarely imposes penalties when manufacturers fail to meet postmarket study commitments.

   Furthermore, given that 522 studies cannot extend beyond 3 years’ duration, important questions about the long-term outcomes of devices cleared via the 510(k) process may remain unanswered.

2. Post-Approval Studies (PAS)—these studies may be ordered as a condition of initial or supplemental approval for high-risk devices regulated via the PMA and HDE pathways. In contrast to 522 Studies, PAS are not subject to limitations in duration and are intended to complement premarket understanding of device safety and effectiveness. Approximately two-thirds of PAS require prospective clinical data collection.

   The FDA has ordered PAS for approximately three-quarters of all high-risk otolaryngologic devices. The majority of these PAS examined long-term outcomes or device performance in patient subgroups under-represented in premarket studies (eg, ethnic minorities and women). PAS may additionally help confirm clinical benefit for new devices. For instance, the FDA approved a hypoglossal nerve stimulator for the treatment of obstructive sleep apnea based on a pivotal study using surrogate primary endpoints (apnea-hypopnea index and oxygen desaturation index) on the condition that the manufacturer conduct a PAS evaluating quality of life measures. Although PAS may greatly inform understanding of device safety (eg, by prompting
manufacturers to withdraw faulty devices from the market), the utility of these studies can be limited by small enrollment numbers, delays in completion, and lack of publicly available findings.\(^6^1\) Furthermore, PAS may not serve as a cost-effective means to assure device safety, given an estimated expenditure of $2 million per study and $150 million per year.\(^6^2\)

**FUTURE DIRECTIONS**

As noted by the FDA,\(^4^4\) traditional methods of premarket and postmarket evaluation may be inadequate to fully understand the risks and benefits of medical devices. Moreover, devices may often be subject to limited postmarket study by manufacturers or independent investigators outside of FDA requirements.\(^6^3^,^6^4\) With these limitations in mind, the FDA recently launched the National Evaluation System for Health Technology, a public-private collaborative aimed at applying advanced analytics to real-world clinical data sources (eg, registries, electronic health records, and claims) to generate insight into device performance across the total product life cycle.\(^4^4\) As the FDA develops enhanced methods of device evaluation, otolaryngologists should understand the current strengths and limitations of regulation and contribute to surveillance efforts (eg, via adverse event reporting or clinical study) to best promote the safe and effective use of these technologies. Moving forward, otolaryngologists may soon be able to leverage a society-sponsored clinical data registry to better promote safe and effective use of devices as part of this initiative.\(^6^5\)

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