Device Safety

Vinay K. Rathi, MD[a,b,*], Stacey T. Gray, MD[a,b]

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

Disclosure Statement: The authors have no conflicts of interest to disclose.
[a] Department of Otolaryngology–Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114, USA; [b] Department of Otolaryngology, Harvard Medical School, Boston, MA, USA
* Corresponding author. Department of Otolaryngology–Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114.
E-mail address: vinay_rathi@meei.harvard.edu

Otolaryngol Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.otc.2018.08.013 **oto.theclinics.com**

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 pathway[7]; 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 1
US Food and Drug Administration regulatory framework for medical devices

Device Class	Risk	Examples	Proportion[a]	Regulatory Controls	Review Pathway	Review Standard
Class I	Low-risk	Tongue depressor Otoscope	67%	General controls	None[b]	None
Class II	Moderate-risk	Ossicular prosthesis Vocal fold injection	31%	General controls and special controls (device-specific)	510(k) process[c]	"Substantial equivalence" to predicate device[d]
Class III	High-risk	Cochlear implant Dermal filler	1%	General controls and PMA	PMA	Clinical evidence of safety and effectiveness
			<1%	General controls and HDE	HDE [e]	Clinical evidence of safety and "probable benefit"

[a] Source: Institute of Medicine. Medical devices and the public's health: the FDA 510(k) clearance process at 35 years. 2011.
[b] Exceptions include select class I devices subject to 510(k) review.
[c] Exceptions include select class II devices exempt from 510(k) review.
[d] Exceptions include class I and class II devices without predicates subject to de novo review.
[e] Reserved for select class III devices indicated for the diagnosis or treatment of uncommon illnesses.

Reproduced from Rathi VK, Gadkaree SK, Ross JS, et al. US Food and Drug Administration clearance of moderate-risk otolaryngologic devices via the 510(k) process, 1997-2016. Otolaryngol Head Neck Surg 2017;157(4):608–17; with permission. ©American Academy of Otolaryngology—Head and Neck Surgery Foundation.

than European policy,[16,17] 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.[18–20]

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.[5] The FDA generally grants clearance on the basis of nonclinical evidence, such as bench testing and technical specifications.[4,10] 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.[11]

The 510(k) pr6ocess has earned much criticism in the wake of recent public health crises related to faulty devices.[18,19] Debate over the 510(k) process has centered around 6 key issues[21]:

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.[22]
2. High-risk device exemptions—until recently, the FDA has allowed manufacturers to market certain high-risk devices, such as mandibular reconstruction plates,[23] 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.[24]
3. Unsafe predicates—manufacturers may obtain clearance on the basis of substantial equivalence to unsafe predicates, including permanently recalled devices.[10] 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.[11]
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.[18,24,25]
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 hydroxylapatite–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.[11] Modified versions of existing devices (eg, design alterations or labeling updates in intended use) account for approximately half of all 510(k) clearances.[11]
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.[11]

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 small[33]; 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 applications[37,39]; 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 lifecycle approach to medical device regulation.[43] 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.[43,44] 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.[44]

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.[45] 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.[46,47] Although providers and patients are not mandated to report adverse device events, the FDA MedWatch program enables voluntary electronic reporting of adverse events.[48] Patients, providers, and other interested parties (eg, researchers) may access adverse event reports through a publicly available online FDA database.[49] Although such reports may prove valuable in identifying safety concerns,[50] 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 of the details of clinical care. As a result, reports often include insufficient information to identify devices and characterize adverse events.[51] Prior work in the field of otolaryngology has demonstrated that variable report quality may preclude meaningful systematic analysis of adverse device events.[52,53]
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.[44,51]
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.[51,54] Furthermore, reporting by patients and providers may be biased by extraneous factors (eg, media coverage).[44]
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 product-specific adverse event rates and hinders the detection of safety concerns.[51]

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,[44] 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[55]:
   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.[56] 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[11]; 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.[23]

   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)[56,57]; nonetheless, the FDA rarely imposes penalties when manufacturers fail to meet postmarket study commitments.[44] 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.[57]
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.[58] 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.[56]

The FDA has ordered PAS for approximately three-quarters of all high-risk otolaryngologic devices.[15] 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.[15,59,60] 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.[61] 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.[62]

FUTURE DIRECTIONS

As noted by the FDA,[44] 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.[63,64] 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.[44] 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.[65]

REFERENCES

1. U.S. Congress. Medical device amendments of 1976. 1976. Available at: https://www.gpo.gov/fdsys/pkg/STATUTE-90/pdf/STATUTE-90-Pg539.pdf. Accessed April 1, 2018.
2. U.S. Food and Drug Administration. Classify your medical device. 2018. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/. Accessed April 1, 2018.
3. U.S. Food and Drug Administration. Regulatory controls. 2018. Available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm#special. Accessed April 1, 2018.
4. Institute of Medicine. Medical devices and the public's health: the FDA 510(k) clearance process at 35 years. 2011. Available at: https://www.nap.edu/read/13150/chapter/6. Accessed April 1, 2018.
5. U.S. Food and Drug Administration. The 510(k) program: evaluating substantial equivalence in premarket notifications. 2014. Available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf. Accessed April 1, 2018.
6. U.S. Food and Drug Administration. Premarket Approval (PMA). 2018. Available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/. Accessed April 1, 2018.
7. U.S. Food and Drug Administration. Humanitarian device exemption. 2018. Available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/humanitariandeviceexemption/default.htm. Accessed April 1, 2018.
8. U.S. Food and Drug Administration. Listing of CDRH Humanitarian Device Exemptions. 2018. Available at: https://www.fda.gov/MedicalDevices/Products

andMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm. Accessed April 1, 2018.
9. U.S. Food and Drug Administration. The least burdensome provisions: concept and principles. Draft guidance for industry and food and drug administration staff. 2017. Available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM588914.pdf. Accessed April 1, 2018.
10. Zuckerman D, Brown P, Das A. Lack of publicly available scientific evidence on the safety and effectiveness of implanted medical devices. JAMA Intern Med 2014;174(11):1781–7.
11. Rathi VK, Gadkaree SK, Ross JS, et al. US Food and Drug Administration Clearance of Moderate-Risk Otolaryngologic Devices via the 510(k) Process, 1997-2016. Otolaryngol Head Neck Surg 2017;157(4):608–17.
12. Hwang TJ, Kesselheim AS, Bourgeois FT. Postmarketing trials and pediatric device approvals. Pediatrics 2014;133(5):e1197–202.
13. Dhruva SS, Bero LA, Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. JAMA 2009;302(24):2679–85.
14. Chen CE, Dhruva SS, Redberg RF. Inclusion of comparative effectiveness data in high-risk cardiovascular device studies at the time of premarket approval. JAMA 2012;308(17):1740–2.
15. Rathi VK, Wang B, Ross JS, et al. Clinical evidence supporting US Food and Drug Administration Premarket approval of high-risk otolaryngologic devices, 2000-2014. Otolaryngol Head Neck Surg 2017;156(2):285–8.
16. Hwang TJ, Sokolov E, Franklin JM, et al. Comparison of rates of safety issues and reporting of trial outcomes for medical devices approved in the European Union and United States: cohort study. BMJ 2016;353:i3323.
17. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. N Engl J Med 2012;366(9):848–55.
18. Ardaugh BM, Graves SE, Redberg RF. The 510(k) ancestry of a metal-on-metal hip implant. N Engl J Med 2013;368(2):97–100.
19. Jacoby VL, Subak L, Waetjen LE. The FDA and the Vaginal Mesh Controversy–Further Impetus to Change the 510(k) Pathway for Medical Device Approval. JAMA Intern Med 2016;176(2):277–8.
20. Hauser RG. Here we go again–another failure of postmarketing device surveillance. N Engl J Med 2012;366(10):873–5.
21. Hines JZ, Lurie P, Yu E, et al. Left to their own devices: breakdowns in United States medical device premarket review. PLoS Med 2010;7(7):e1000280.
22. U.S. Food and Drug Administration. 510(k) Premarket Notification for Relieva Sinus Balloon Dilation Catheter. 2005. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf4/K043527.pdf. Accessed April 1, 2008.
23. U.S. Food and Drug Administration. 522 Postmarket Surveillance Study Status: Hummingbird tympanostomy tube system. 2018. Available at: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm240318.htm. Accessed April 23, 2018.
24. Rathi VK, Kesselheim AS, Ross JS. The US Food and Drug Administration 515 Program Initiative: addressing the evidence gap for widely used, high-risk cardiovascular devices? JAMA Cardiol 2016;1(2):117–8.
25. Chatterjee S, Herrmann HC, Wilensky RL, et al. Safety and procedural success of left atrial appendage exclusion with the lariat device: a systematic review of

published reports and analytic review of the FDA MAUDE database. JAMA Intern Med 2015;175(7):1104–9.
26. Challoner D, Vodra WW. Medical devices and health–creating a new regulatory framework for moderate-risk devices. N Engl J Med 2011;365(11):977–9.
27. Garber AM. Modernizing device regulation. N Engl J Med 2010;362(13):1161–3.
28. Gottieb S, Shuren J. New steps to facilitate beneficial medical device innovation. 2017. Available at: https://blogs.fda.gov/fdavoice/index.php/tag/new-pre-and-post-market-evaluation-system-nest/. Accessed April 29, 2018.
29. Phillips PJ. Sufficiency of information in 510(k) summaries. JAMA Intern Med 2015;175(5):863–4.
30. U.S. Food and Drug Administration. Investigational device exemptions (IDEs) for early feasibility medical device clinical studies, including certain first in human (FIH) studies: guidance for industry and FDA staff. 2013. Available at: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf. Accessed April 1, 2018.
31. U.S. Food and Drug Administration. Design considerations for pivotal clinical investigations for medical devices: guidance for industry, clinical investigators, institutional review boards and FDA staff. 2013. Available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf. Accessed April 1, 2018.
32. Downing NS, Aminawung JA, Shah ND, et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. JAMA 2014;311(4):368–77.
33. Faris O, Shuren J. An FDA viewpoint on unique considerations for medical-device clinical trials. N Engl J Med 2017;376(14):1350–7.
34. Dhruva SS, Mazure CM, Ross JS, et al. Inclusion of demographic-specific information in studies supporting US Food & Drug Administration approval of high-risk medical devices. JAMA Intern Med 2017;177(9):1390–1.
35. U.S. Food and Drug Administration. FDA action plan to enhance the collection and availability of demographic subgroup data. 2014. Available at: https://www.fda.gov/downloads/regulatoryinformation/legislation/significantamendmentstothefdcact/fdasia/ucm410474.pdf. Accessed April 1, 2018.
36. U.S. Food and Drug Administration. PMA Supplements and Amendments. 2018. Available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050467.htm. Accessed April 1, 2018.
37. Rome BN, Kramer DB, Kesselheim AS. FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979-2012. JAMA 2014;311(4):385–91.
38. Rathi VK, Ross JS, Samuel AM, et al. Postmarket modifications of high-risk therapeutic devices in otolaryngology cleared by the US Food and Drug Administration. Otolaryngol Head Neck Surg 2015;153(3):400–8.
39. Samuel AM, Rathi VK, Grauer JN, et al. How do orthopaedic devices change after their initial FDA premarket approval? Clin Orthop 2016;474(4):1053–68.
40. Zheng SY, Redberg RF. Premarket approval supplement pathway: do we know what we are getting? Ann Intern Med 2014;160(11):798–9.
41. Hildrew DM, Molony TB. Nucleus N5 CI500 series implant recall: hard failure rate at a major Cochlear implantation center. Laryngoscope 2013;123(11):2829–33.
42. Arnold W, Bredberg G, Gstöttner W, et al. Meningitis following cochlear implantation: pathomechanisms, clinical symptoms, conservative and surgical treatments. ORL J Otorhinolaryngol Relat Spec 2002;64(6):382–9.

43. U.S. Food and Drug Administration. Balancing premarket and postmarket data collection for devices subject to premarket approval: guidance for industry and food and drug administration staff. 2015. Available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393994.pdf. Accessed April 1, 2018.
44. Shuren J, Califf RM. Need for a national evaluation system for health technology. JAMA 2016;316(11):1153–4.
45. U.S. Food and Drug Administration. Mandatory reporting requirements: manufacturers, importers and device user facilities. 2018. Available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm. Accessed April 14, 2018.
46. U.S. Food and Drug Administration. MedSun: Medical product safety network. 2018. Available at: https://www.fda.gov/MedicalDevices/Safety/MedSunMedicalProductSafetyNetwork/default.htm?source=govdelivery. Accessed April 14, 2018.
47. Engleman D, Rich S, Powell T, et al. Medical Product Safety Network (MedSun) Collaborates with medical product users to create specialty subnetworks. In: Henriksen K, Battles JB, Keyes MA, et al, editors. Advances in patient safety: new directions and alternative approaches, vol. 1: Assessment. Rockville (MD): Agency for Healthcare Research and Quality; 2008. p. 1–12.
48. U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. 2018. Available at: https://www.fda.gov/Safety/MedWatch/. Accessed April 14, 2018.
49. U.S. Food and Drug Administration. MAUDE - Manufacturer and User Facility Device Experience. 2018. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/TextSearch.cfm. Accessed April 14, 2018.
50. Woerdeman PA, Cochrane DD. Disruption of silicone valve housing in a Codman Hakim Precision valve with integrated Siphonguard. J Neurosurg Pediatr 2014;13(5):532–5.
51. Rajan PV, Kramer DB, Kesselheim AS. Medical device postapproval safety monitoring: where does the United States stand? Circ Cardiovasc Qual Outcomes 2015;8(1):124–31.
52. Coelho DH, Tampio AJ. The utility of the MAUDE database for osseointegrated auditory implants. Ann Otol Rhinol Laryngol 2017;126(1):61–6.
53. Tambyraja RR, Gutman MA, Megerian CA. Cochlear implant complications: utility of federal database in systematic analysis. Arch Otolaryngol Head Neck Surg 2005;131(3):245–50.
54. Lenzer J, Brownlee S. Why the FDA can't protect the public. BMJ 2010;341:c4753.
55. U.S. Food and Drug Administration. 522 Postmarket Surveillance Studies – Frequently Asked Questions (FAQs). 2018. Available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostmarketSurveillance/ucm134497.htm. Accessed April 28, 2018.
56. U.S. Government Accountability Office. FDA ordered postmarket studies to better understand safety issues, and many studies are ongoing. 2015. Available at: http://www.gao.gov/assets/680/672860.pdf. Accessed April 28, 2018.
57. Rising JP, Reynolds IS, Sedrakyan A. Delays and difficulties in assessing metal-on-metal hip implants. N Engl J Med 2012;367(1):e1.
58. U.S. Food and Drug Administration. Procedures for Handling Post-Approval Studies Imposed by PMA Order. 2009. Available at: https://www.fda.gov/MedicalDevices/ucm070974.htm. Accessed April 28, 2018.

59. U.S. Food and Drug Administration. Summary of safety and effectiveness data: inspire upper airway stimulation. 2014. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008B.pdf. Accessed April 28, 2018.
60. U.S. Food and Drug Administration. Premarket approval order: inspire upper airway stimulation. 2014. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008A.pdf. Accessed April 28, 2018.
61. Reynolds IS, Rising JP, Coukell AJ, et al. Assessing the safety and effectiveness of devices after US Food and Drug Administration approval: FDA-mandated post-approval studies. JAMA Intern Med 2014;174(11):1773–9.
62. Wimmer NJ, Robbins S, Ssemaganda H, et al. Assessing the cost burden of United States FDA-mandated post-approval studies for medical devices. J Health Care Finance 2016;2016(Spec Features) [pii:http://www.healthfinancejournal.com/~junland/index.php/johcf/article/view/82/83].
63. Rathi VK, Krumholz HM, Masoudi FA, et al. Characteristics of clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving FDA premarket approval in 2010 and 2011. JAMA 2015;314(6):604–12.
64. Rathi VK. Clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving US Food and Drug Administration Premarket Approval in 2010 and 2011 [doctorate thesis]. New Haven (CT): Yale University; 2016.
65. Denneny JC. Regent: a new otolaryngology clinical data registry. Otolaryngol Head Neck Surg 2016;155(1):5.