VIEWPOINT

Moving From Substantial Equivalence to Substantial Improvement for 510(k) Devices

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Medical devices have been receiving more public attention and scrutiny in recent years because of safety problems. A 2018 Netflix documentary, *The Bleeding Edge*, highlighted multiple such medical devices, 2 of which, Essure (a device for female sterilization) and transvaginal mesh for pelvic organ prolapse, were taken off the market after the film's release. Recent *Kaiser Health News* stories reported that more than 1 million medical device adverse event reports had been sealed from public view by the US Food and Drug Administration (FDA).[1] *The New York Times* recently called for reforms in device regulation in an editorial entitled "80,000 Deaths. 2 Million Injuries. It's Time for a Reckoning on Medical Devices."[2]

The FDA premarket review pathway that accounts for a disproportionate number of the recalls for the most serious risks is called 510(k), and this pathway is also the most frequently used for clearance of medical devices. The 510(k) pathway allows a new medical device to come to market if it is "substantially equivalent" to a predicate device(s). A predicate device is one that is currently available or has been cleared by the FDA for the US market for the same intended use. "Substantial equivalence" can be based on similarity to pieces of multiple predicate devices, even devices removed from the market because of ineffectiveness or lack of safety; clinical data are not required, although the FDA may ask for it, and 8% of 510(k) submissions for non–in vitro diagnostic devices contain clinical data.[3] Although the 510(k) pathway is meant for moderate-risk devices, malfunction or defects in 510(k) devices do lead to severe harms or deaths. For example, duodenoscopes, used in more than half a million US procedures annually, received 510(k) clearance and have been associated with the transmission of multiple multidrug-resistant bacteria outbreaks and patient deaths.[4]

In 2011, at the request of the FDA, the Institute of Medicine (IOM, now the National Academy of Medicine [NAM]) examined the 510(k) pathway. The report concluded that, with some exceptions, 510(k) clearance was "not intended to evaluate the safety and effectiveness of medical devices" (only substantial equivalence), nor whether a new device is innovative.[3] The IOM/NAM recommended replacing the pathway with a system that integrated premarket and postmarket data with the goals of both ensuring that devices are available in a timely manner as well as safety and effectiveness throughout the device's life cycle. To achieve this goal, the IOM/NAM recommended that the FDA implement a comprehensive strategy to obtain, analyze, and act on postmarket medical device information.

Late in 2018, the FDA announced the goal of "ensuring that the FDA is consistently first among the world's regulatory agencies to identify and act upon safety signals related to medical devices."[5] The 2011 report from the IOM/NAM found that some device recalls could have been identified with rigorous premarket review, but most were triggered by postmarket events. Therefore, both premarket and postmarket review must be strengthened to ensure that patients are receiving safer and more effective devices.

For premarket review of 510(k) devices, on February 1, 2019, the FDA released a Final Guidance Document for the "Safety and Performance Based Pathway."[6] This optional pathway consists of using criteria that involve conformance to FDA-recognized consensus standards, FDA guidance, and/or special controls. It enables 510(k) clearance for certain medical devices if the device meets these specific criteria, which should include safety and effectiveness (as opposed to the often ill-defined "substantial equivalence" to predicate devices). The decision to use this new pathway is determined by manufacturers, although the FDA can disagree with this determination.

Although less use of "substantial equivalence" to predicate devices, which cannot ensure safety and effectiveness, is a step in the right direction, there are more opportunities for improvements without compromising innovation. Legislation is needed to require that 510(k) devices use this new pathway within 5 years, thereby eliminating use of predicates. Furthermore, legislation should mandate that 510(k) devices show improved safety and effectiveness compared with marketed devices for the same clinical purpose, using meaningful clinical criteria to gain clearance. Although these criteria will differ based on the intended use of the device, all criteria should be based on patient-oriented clinical outcomes.

Because of the small size and limited follow-up of most trials compared with device use in clinical practice, safety concerns may not be detected through premarket review. For example, a bioresorbable vascular scaffold was approved in 2016 based on 1-year follow-up data in a noninferiority trial compared with drug-eluting stents. However, postapproval clinical trial data demonstrated that the device had higher major adverse cardiac event rates compared with drug-eluting stents in long-term follow-up; the manufacturer soon thereafter decided to halt device sales.

Because many safety issues only emerge once a product is in clinical use, postmarket surveillance for all medical devices must be strengthened. The growing emphasis on priority review and shortening premarket time makes postmarket surveillance critical for safety and effectiveness. Currently, the FDA often relies on mandated postmarketing studies and passive surveillance through adverse event reports; both methods have many limitations. Current adverse event reporting is estimated to represent a small fraction of actual adverse event occurrences. Still, adverse event reports have provided signals for some important safety concerns. The sealing of more than 1 million

adverse event reports from public view by the FDA for multiple devices[1] was concerning, and there was a clear call for immediate and strong action to end this policy; the FDA has indicated that it will do so.[7]

Postmarket surveillance would be strengthened by time-limited conditional approval for medical devices of 1 or 2 years, with preplanned criteria that would need to be met based on postmarket data to ensure that the device met acceptable clinical safety and effectiveness thresholds to remain on the market. All device usage would occur only in the context of data collection from clinical practice settings. Although this is a challenging and complex task, the National Evaluation System for Health Technology (NEST) is being developed to assess the safety of devices in clinical practice settings.[8] NEST is working with 12 network collaborators to explore the use of data from clinical registries, electronic health records and medical billing claims for regulatory submissions. The activities of NEST include implementing tools for active surveillance of medical devices to address the current limitations of postmarket surveillance.

Because coverage is necessary to support use of devices in clinical practice, more use of the coverage with evidence development approach would allow rapid accrual of safety and effectiveness data. Coverage with evidence development has been used successfully, such as by the Lung Volume Reduction Study, which investigated a promising new procedure for treatment of chronic obstructive pulmonary disease.[9] Medicare required clinical trial enrollment for coverage, which led to rapid enrollment of patients to evaluate the procedure. Other countries, such as Japan, require certain high-risk devices to refile approval applications several years after initial approval, during which additional data are reviewed. Successful implementation of such a strategy means that the Unique Device Identifier must be integrated into health information sources, therefore allowing device tracking. Established prospective, active surveillance methods could then be applied to detect safety signals. While the sheer number of medical devices that come to market (thousands annually), along with their frequent iterative modifications, makes this a challenging endeavor, the increasing availability of large volumes of electronic health data make it increasingly feasible to study device safety and effectiveness, and the long-term goal should be to ensure that all devices have appropriate clinical evaluation.

Most importantly, devices that receive conditional approval must be removed from the market if clinical evidence either (1) demonstrates that they are not both safe and effective or (2) does not definitively demonstrate that they are safe and effective. To the first point, predetermined clinically meaningful criteria would need to be met to ensure that a device could remain on the market. To the second point, data would need to be generated through preplanned clinical studies that examine all uses (both on label and off label). If such data are not generated within a timely, agreed-on, and publicly available schedule, then the device's conditional approval would end. The FDA has never withdrawn device approval owing to failure to comply with mandated postmarketing surveillance,[10] which weakens the postmarket surveillance system. Actions such as the FDA's April 2019 order to manufacturers to stop marketing all surgical mesh intended for pelvic organ prolapse repair because safety and effectiveness were not demonstrated are necessary to protect patient safety.

More than 4 decades after the FDA gained the prerogative to regulate medical devices, the renewed attention to ensuring safety and effectiveness presents an important opportunity to strengthen regulation of 510(k) devices. Legislation that required each device be an improvement over currently available devices based on objective criteria would promote innovation. Mandating postmarket data from clinical practice based on objective criteria for safety and effectiveness could improve the care of the millions of patients in whom a medical device may be used.

ARTICLE INFORMATION

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REFERENCES

1. Jewett C. Hidden FDA reports detail harm caused by scores of medical devices. *Kaiser Health News*. March 7, 2019. https://khn.org/news/hidden-fda-database-medical-device-injuries-malfunctions/. Accessed June 5, 2019.

2. 80,000 deaths. 2 million injuries. It's time for a reckoning on medical devices. *New York Times*. May 4, 2019. https://www.nytimes.com/2019/05/04/opinion/sunday/medical-devices.html. Accessed July 19, 2019.

3. Institute of Medicine. *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*. July 29, 2011. http://www.nationalacademies.org/hmd/Reports/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years.aspx Accessed July 19, 2019.

4. US Food and Drug Administration. Infections associated with reprocessed duodenoscopes. https://www.fda.gov/medical-devices/reprocessing-reusable-medical-devices/infections-associated-reprocessed-duodenoscopes. Accessed June 5, 2019.

5. US Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, MD and Jeff Shuren, MD, director of the Center for Devices and Radiological Health, on FDA's updates to Medical Device Safety Action Plan to enhance post-market safety. November 20, 2018. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-jeff-shuren-md-director-center-devices-and-2. Accessed July 19, 2019.

6. US Food and Drug Administration. *Safety and Performance Based Pathway: Guidance for Industry and Food and Drug Administration*. February 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-and-performance-based-pathway. Accessed July 19, 2019.

7. US Food and Drug Administration. Statement from FDA Principal Deputy Commissioner Amy Abernethy, MD, PhD, and Jeff Shuren, MD, JD, director of the FDA's Center for Devices and Radiological Health on FDA's new efforts to protect women's health and help to ensure the safety of breast implants. May 2, 2019. https://www.fda.gov/news-events/press-announcements/statement-fda-principal-deputy-commissioner-amy-abernethy-md-phd-and-jeff-shuren-md-jd-director-fdas. Accessed July 19, 2019.

8. Shuren J, Califf RM. Need for a National Evaluation System for Health Technology. *JAMA*. 2016;316(11):1153-1154. doi:10.1001/jama.2016.8708

9. Fishman A, Martinez F, Naunheim K, et al; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med*. 2003;348(21):2059-2073. doi:10.1056/NEJMoa030287

10. Reynolds IS, Rising JP, Coukell AJ, Paulson KH, Redberg RF. Assessing the safety and effectiveness of devices after US Food and Drug Administration approval: FDA-mandated postapproval studies. *JAMA Intern Med*. 2014;174(11):1773-1779. doi:10.1001/jamainternmed.2014.4194