16

Ensuring Patient Safety and Benefit in Use of Medical Devices Granted Expedited Approval

Sanket S. Dhruva, Jonathan J. Darrow, Aaron S. Kesselheim, and Rita F. Redberg

In recent years, legislative mandates and regulatory policy in the United States have sought to streamline testing and approval requirements for novel medical devices with the goal of lowering development costs and accelerating market entry. But increasingly flexible approval requirements mean greater uncertainty as to the extent to which authorized medical devices will benefit patients without unforeseen risks. Some authorized medical devices have later been found to have safety or effectiveness concerns, but once a product is marketed it can be difficult for regulators to take remedial action. There are several reasons for this, including a reluctance to engage in regulatory self-reversal; physician and patient enthusiasm for novel technologies; generous payor coverage that provides higher margins; the challenges of conducting randomized postmarket clinical trials; and the effectiveness of devices in some, but not necessarily most or all, clinical settings. To address these reasons for inadequate regulatory response and better ensure that patients benefit from medical devices approved through special development pathways, we recommend that current expedited development or approval programs be contingent upon 1) timely progress of mandatory postmarket studies and 2) clinical data from these postmarket studies demonstrating that the threshold of reasonable assurance of safety and effectiveness is met for the primary endpoints. Until postmarket studies are completed, improved disclosure to patients is necessary to ensure they are able to provide informed consent.

16.1 BACKGROUND

The availability of medical devices in the United States is overseen by the Food and Drug Administration (FDA), which evaluates new devices under a framework established by the 1976 Medical Device Amendments.[1] Under this law, devices are classified into three tiers, with the rigor of regulatory review commensurate with anticipated risk to patients. The highest-risk devices (Class III) are subject to the

[1] Medical Device Regulation Act, Pub. L. No. 94–295, 90 Stat. 539 (1976).

https://doi.org/10.1017/9781108975452.017 Published online by Cambridge University Press

FDA's most stringent review process, called Premarket Approval (PMA),[2] and are required to demonstrate a reasonable assurance of safety and effectiveness to receive marketing authorization. More flexible standards are applied to lower-tier devices (Class I and II), many of which are exempt from review altogether. Since the FDA Modernization Act of 1997, the FDA must consider the "least burdensome" means of evaluating medical devices, defined in FDA guidance as "the minimum amount of information necessary to adequately address a relevant regulatory question."[3]

While this regulatory framework has helped steward new devices that benefit patients onto the market, it has also allowed for the marketing of unsafe and ineffective medical devices, some of which have remained on the market for years. Even for devices subject to PMA, rigorous high-quality evidence is not necessarily required.[4] Studies have found low rates of randomization and blinding (i.e. allocation concealment among involved individuals) among clinical trials supporting approval of such devices.[5] Trials are often single-arm, with comparison to historical (instead of active) controls, which can lead to biased estimates of treatment effects.[6] Surrogate measures used in pivotal trials often do not translate to meaningful clinical improvements.[7] "Training patients," which allow clinicians to gain experience using or implanting a device, are often excluded from reported clinical trial results, widening the gap between labeled efficacy and real-world

[2] US Food & Drug Admin., Premarket Approval (PMA), https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma.

[3] US Food & Drug Admin., The Least Burdensome Provisions: Concept and Principles; Guidance for Industry and Food and Drug Administration Staff, https://www.fda.gov/media/73188/download.

[4] Sanket S. Dhruva et al., Strength of Study Evidence Examined by the FDA in Premarket Approval of Cardiovascular Devices, 302 JAMA 2679 (2009); Connie E. Chen et al., Inclusion of Training Patients in US Food and Drug Administration Premarket Approval Cardiovascular Device Studies, 171 Arch. Intern. Med. 534 (2011); Sanket S. Dhruva et al., Gender Bias in Studies for Food and Drug Administration Premarket Approval of Cardiovascular Devices, 4 Circ. Cardiovasc. Qual. Outcomes 165 (2011); Connie E. Chen et al., Inclusion of Comparative Effectiveness Data In High-Risk Cardiovascular Device Studies at the Time of Premarket Approval, 308 JAMA 1740 (2012); Vinay K. Rathi 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, 314 JAMA 604 (2015); Benjamin N. Rome et al., FDA Approval of Cardiac Implantable Electronic Devices Via Original and Supplement Premarket Approval Pathways, 1979–2012, 311 JAMA 385 (2014); Sanket S. Dhruva et al., Revisiting Essure–Toward Safe and Effective Sterilization, 373 N. Engl. J. Med. (2015); Rita F. Redberg, Sham Controls in Medical Device Trials, 371 N. Engl. J. Med. 892 (2014); Sarah Y. Zheng et al., Characteristics of Clinical Studies Used for US Food and Drug Administration Approval of High-Risk Medical Device Supplements, 318 JAMA 619 (2017); Rita F. Redberg & Sanket S. Dhruva, The F.D.A.'s Medical Device Problem [Op-Ed], N.Y. Times (July 17, 2015), https://www.nytimes.com/2015/07/17/opinion/the-fdas-medical-device-problem.html; L. Camille Jones et al., Assessment of Clinical Trial Evidence for High-Risk Cardiovascular Devices Approved Under the Food and Drug Administration Priority Review Program, 178 JAMA Intern. Med. 1418 (2018).

[5] Dhruva et al., supra note 4; Zheng et al., supra note 4; L. Camille Jones et al., supra note 4.

[6] H. Sacks et al., Randomized Versus Historical Controls for Clinical Trials, 72 Am. J. Med. 233 (1982).

[7] William S. Weintraub et al., The Perils of Surrogate Endpoints, 36 Eur. Heart J. 2212 (2015).

effectiveness.[8] Trials often include small numbers of selected patients that may not represent the diversity of real-world patients, for example, due to the exclusion of older adults, women, or those with co-morbidities.[9] Trial followup is commonly short – an important limitation because many of these devices are permanently implanted, but safety concerns may not be apparent until years after approval.

Evidence limitations for 510(k) cleared devices are even greater.[10] This commonly used process is based on "substantial equivalence" to one or more predicate (i.e. previously available) medical devices.[11] Aware that the predicates on which equivalence was based had no requirement for safety or effectiveness, Congress recognized early on that the substantial equivalence requirement of the 510(k) clearance process did not provide full assurance of safety and effectiveness.[12] In 2011, the Institute of Medicine drew attention to this concern and recommended replacing the pathway,[13] which has been responsible for the highest proportion of medical device recalls.[14]

Given the limitations in clinical evidence leading to uncertainties of benefit and risk at the time of approval, medical devices might be expected to undergo timely and rigorous postapproval evaluation. Yet only 54 out of 792 (or 7 percent) postapproval studies ordered between 1991 and 2020 were randomized clinical trials,[15] and of 28 PMA devices approved from 2010–2011, only 13 percent of 204 FDA-required or manufacturer/investigator-initiated postapproval studies were completed between three and five years after FDA approval.[16] Even eight to ten years after approval, only one-third were completed with final results reported on clinicaltrials.gov or in peer-reviewed publications.[17] The FDA has never issued a warning letter or penalty because of study delays or inadequate progress of a medical device postapproval study.[18]

[8] Connie E. Chen et al., supra note 4.
[9] Dhruva et al. (2011), supra note 4.
[10] Rita F. Redberg & Sanket S. Dhruva, Moving from Substantial Equivalence to Substantial Improvement for 510(k) Devices, 322 JAMA 927 (2019).
[11] Supra note 1.
[12] H. Comm. Energy & Commerce, Subcommittee on Oversight and Investigations, Medical Device Regulation: the FDA's Neglected Stepchild: an Oversight Report on FDA Implementation of the Medical Device Amendments of 1976 (1983).
[13] Institute of Medicine, Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years (2011), https://www.nap.edu/catalog/13150/medical-devices-and-the-publics-health-the-fda-510k-clearance.
[14] Diana M. Zuckerman et al., Medical Device Recalls and the FDA Approval Process, 171 Arch. Intern. Med. 1006 (2011).
[15] Jonathan J. Darrow et al., 326 FDA Regulation and Approval of Medical Devices: 1976–2019 420 (2021).
[16] Rathi et al., supra note 4.
[17] Vinay K. Rathi et al., Postmarket Clinical Evidence for High-Risk Therapeutic Medical Devices Receiving Food and Drug Administration Premarket Approval in 2010 and 2011, 3 JAMA Netw. Open (2020).
[18] Ian S. Reynolds et al., Assessing the Safety and Effectiveness of Devices after US Food and Drug Administration Approval: FDA-mandated Postapproval Studies, 174 JAMA Intern. Med. 1773 (2014).

Limited pre and postmarket evidence can expose patients to unnecessary harm by allowing the availability of unsafe and/or ineffective medical devices. For example, in 2002 the Essure hysteroscopic sterilization device received premarket approval based on surrogate measures with short (up to two years) followup duration in just 926 women and was subsequently implanted in approximately 750,000 women. Postapproval studies were either not completed or terminated early.[19] Serious adverse events, including bleeding, pain, and unintended pregnancies were reported by thousands of women. The FDA responded by requiring new studies, and the device was eventually voluntarily removed from the market by its manufacturer in 2018 – sixteen years after FDA approval and just months after the Netflix documentary, *The Bleeding Edge*, documented the dangers of Essure and other currently used medical devices.[20]

16.2 INCREASING UNCERTAINTY ABOUT RISKS AND BENEFITS OF MARKETED MEDICAL DEVICES AT THE TIME OF CLEARANCE OR APPROVAL

Despite the limited clinical evidence supporting medical device clearance and approvals, legislative mandates, such as the 2016 21st Century Cures Act's codification of the Breakthrough Devices Program,[21] increase the potential for uncertainty of risks and benefits. These new flexibilities represent Congressional responses to concerns that device availability in the United States sometimes lags behind access abroad.[22]

But new legislation has not been accompanied by rigorous eligibility requirements that would protect patients. For example, devices may qualify for Breakthrough status if "availability is in the best interest of patients," providing the FDA with virtually unbounded discretion.[23] The agency has explicitly acknowledged that accelerating device approvals can reduce certainty of benefit. Agency guidance for the Breakthrough Devices Program, for example, states that the FDA "may accept a greater extent of uncertainty of the benefit-risk profile for these devices if appropriate under the circumstances."[24] Devices approved through expedited pathways are more likely to be approved based on lower-quality evidence, such as trials that lack randomization or blinding, use surrogate measures, or are of limited

[19] Sanket S. Dhruva et al., supra note 4.

[20] Akshay Pendyal & Joseph R. Ross, The Bleeding Edge: Documenting Innovation and Injury in the Medical Device Industry, 322 JAMA 190 (2019).

[21] 21st Century Cures Act, PL 114–255 (Dec. 13, 2016); Aaron S. Kesselheim & Thomas J. Hwang, Breakthrough Medical Devices and the 21st Century Cures Act, 164 Ann. Intern. Med. 500 (2016); US Food & Drug Admin., Breakthrough Devices Program: Guidance for Industry and Food and Drug Administration Staff, https://www.fda.gov/media/108135/download.

[22] David R. Holmes et al., Clinical Perspective–Early Feasibility Device Medical Studies in the United States: Time for More Than Regulatory Reform, 9 JACC Cardiovasc. Interv. 626 (2016).

[23] 21st Century Cures Act, supra note 21.

[24] US Food & Drug Admin., supra note 21.

duration.[25] A recent study of fifteen "breakthrough" devices found that two of these had been cleared under the 510(k) pathway,[26] a seemingly incongruous designation given that this pathway requires the 510(k) cleared device to be "substantially equivalent" to its previously marketed predicate. The paradox may be explained, if not necessarily justified, by the low and flexible bar to breakthrough designation and the generous definition of "substantial equivalence," which encompasses devices with "significant changes" in materials, design, energy source, or other features as compared to the predicate, so long as they do not raise different questions of safety or effectiveness.[27]

Due to the high costs of some devices, payor coverage must follow FDA authorization before widespread use is feasible. Payors can therefore serve as important gatekeepers against potentially unsafe or ineffective devices by restricting coverage until higher-quality evidence of benefit is generated. But payor oversight has been scaled back as well. Since late 2019, the Centers for Medicare and Medicaid Services (CMS) has been providing New Technology Add-On Payments for all FDA-designated Breakthrough Devices and increased reimbursement,[28] while waiving its longstanding (nineteen years) criterion that devices eligible for such add-on payments actually provide "substantial clinical improvement."[29] Increasing reimbursement without high-quality evidence of patient benefit means that such data are not likely to ever be generated, as FDA approval and insurer coverage are strong incentives for conducting new high-quality trials.

The COVID-19 pandemic has accelerated the trend toward lower evidentiary thresholds. For example, in August 2020, the Impella® (Abiomed, Danvers, MA), a mechanical circulatory support device, received Emergency Use Authorization (EUA) for patients who experience complications while receiving extracorporeal membrane oxygenation,[30] despite limited established efficacy for this indication. EUA is a mechanism authorized by Congress in 2004 that allows widespread preapproval access for drugs or medical devices that "may be effective" in case of

[25] Jones et al., supra note 5; Early Experience with the FDA's Breakthrough Devices Program, 38 Nat. Biotechnol. 933 (2020).

[26] James L. Johnston et al., infra note 25.

[27] US Food & Drug Admin., The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]; Guidance for Industry and Food and Drug Administration Staff, https://www.fda.gov/media/82395/download.

[28] Centers for Medicare & Medicaid Services, Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals (2019), https://www.federalregister.gov/documents/2019/08/16/2019-16762/medicare-program-hospital-inpatient-prospective-payment-systems-for-acute-care-hospitals-and-the.

[29] Timothy J. Judson et al., Evaluation of Technologies Approved for Supplemental Payments in the United States, 365 BMJ (Clinical research ed). (2019).

[30] Abiomed, FDA Issues Emergency Use Authorization for Impella Heart Pumps to Provide Unloading Therapy to COVID-19 Patients, https://investors.abiomed.com/investors/press-releases/news-details/2020/FDA-Issues-Emergency-Use-Authorization-for-Impella-Heart-Pumps-to-Provide-Unloading-Therapy-to-COVID-19-Patients-08-04-2020/default.aspx.

declared emergencies associated with chemical, biological, radiological, or nuclear threats. Another similar device, the Impella RP®, received EUA in June 2020 for patients with COVID-19-related right-sided heart failure.[31] Emergency use was authorized even though a May 2019 "Dear Doctor" letter advised that fewer than 30 percent of patients receiving the device in a postapproval trial for a different indication lived to thirty days, hospital discharge, or to the start of next longer term therapy (this proportion of real-world survival was much lower than in premarket clinical studies, which had demonstrated that 73.3 percent survived to thirty days, hospital discharge, or the start of longterm therapy).[32] It was subsequently determined that lower survival was among patients who would not have qualified for premarket clinical studies.

16.3 LACK OF REGULATORY ACTION FOR UNSAFE DEVICES

While the FDA has the authority to revoke device approval, the agency has generally chosen to regulate with a lighter touch. In the rare cases when unsafe or ineffective devices have been removed from the market, manufacturers have done so voluntarily in the shadow of mandatory FDA recall authority, sometimes citing declining sales and possibly motivated by litigation concerns. The previously mentioned discontinuation of the Essure hysteroscopic sterilization device by its manufacturer in 2018 is one example.[33] In other cases, the FDA has imposed new evidence requirements that may have contributed to voluntary withdrawal. For example, after metal-on-metal orthopedic hips were found to have serious adverse events, including the release of metal ions into the bloodstream and adverse local tissue reactions that can lead to pain and device failure,[34] the FDA issued a final order in 2016 that required removal from market within ninety days if a PMA had not been filed for metal-on-metal hips marketed at that time.[35] All manufacturers have voluntarily stopped marketing these devices.[36]

[31] Abiomed, FDA Issues Emergency Use Authorization for Impella RP as Therapy for COVID-19 Patients with Right Heart Failure, https://investors.abiomed.com/investors/press-releases/news-details/2020/FDA-Issues-Emergency-Use-Authorization-for-Impella-RP-as-Therapy-for-COVID-19-Patients-with-Right-Heart-Failure-06-01-2020/default.aspx.

[32] US Food & Drug Admin., Increased Rate of Mortality in Patients Receiving Abiomed Impella RP System – Letter to Health Care Providers,https://www.fda.gov/medical-devices/letters-health-care-providers/update-increased-rate-mortality-patients-receiving-abiomed-impella-rp-system-letter-health-care.

[33] US Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on manufacturer announcement to halt Essure sales in the US; agency's continued commitment to postmarket review of Essure and keeping women informed, https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-manufacturer-announcement-halt-essure-sales-us-agencys.

[34] US Food & Drug Admin., Concerns about Metal-on-Metal Hip Implants, https://www.fda.gov/medical-devices/metal-metal-hip-implants/concerns-about-metal-metal-hip-implants.

[35] Effective date of requirement for Premarket Approval for total metal-on-metal semi-constrained hip joint systems, 21 C.F.R. § 888 (2016).

[36] US Food & Drug Admin., Metal-on-Metal Hip Implants: The FDA's Activities, https://www.fda.gov/medical-devices/metal-metal-hip-implants/metal-metal-hip-implants-fdas-activities.

In other cases, the agency has not taken regulatory action even when studies with FDA involvement showed that the devices were associated with increased mortality. For example, paclitaxel-coated balloons and stents are sometimes used during endovascular intervention among patients with femoropopliteal peripheral artery disease. A meta-analysis using individual patient data, which followed FDA guidance and had a statistical analysis plan "based on formal discussions with the US Food and Drug Administration with review and approval by industry members," found these devices were associated with a 4.6 percent absolute increase in in-hospital mortality compared to patients receiving standard balloon angioplasty.[37] The FDA concluded that additional clarification was needed,[38] but has not yet taken any regulatory action to restrict use.

The FDA has, at times, revised device labeling or recommended narrower indications in an effort to address safety issues while also minimizing disruptions to the market. For the Essure hysteroscopic sterilization device, the FDA promulgated guidance that included a "patient decision checklist" intended for both patient and physician signature that contained specific information about risks and benefits[39]. Measures such as this are intended to bolster informed consent so that patients are able to exercise appropriate autonomy when deciding whether to have the device implanted. The Wingspan intracranial stent system (Stryker Neurovascular, Kalamazoo, MI) received a Humanitarian Device Exemption approval by the FDA in 2005 based on a single-arm study that enrolled forty-five patients, with outcomes compared to historical controls at thirty days.[40] However, a subsequent randomized trial found that the Wingspan device had an increased risk of the composite endpoint of stroke or death in comparison to medical therapy.[41] Despite these findings, the FDA did not rescind the Humanitarian Device Exemption approval. Instead, the agency left the device on the market so that it would be available as an option for patients similar to those in the initial single-arm study of forty-five patients,[42] even though that study had significant limitations in rigor. Because the FDA does not regulate the practice of medicine, physicians can continue to use these medical devices off-label for patients who do not meet FDA-recommended criteria. To address safety concerns, the FDA issued a Safety

[37] Krishna J. Rocha-Singh et al., Mortality and Paclitaxel-Coated Devices: An Individual Patient Data Meta-Analysis, 141 Circulation 1859 (2020).

[38] Sara Royce et al., US Food and Drug Administration Perspective on "Mortality and Paclitaxel-Coated Devices: An Individual Patient Data Meta-Analysis," 141 Circulation 1870 (2020).

[39] US Food & Drug Admin., supra note 31; US Food & Drug Admin., Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization; Guidance for Industry and Food and Drug Administration Staff, https://www.fda.gov/media/96315/download.

[40] Ari J. Gartenberg et al., Presumed Safe No More: Lessons from the Wingspan Saga on Regulation of Devices, 348 BMJ (Clinical research ed). (2014).

[41] Marc I. Chimowitz et al., Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis, 365 N. Engl. J. Med. 993 (2011).

[42] Gartenberg et al., supra note 40.

Communication in 2019 (fourteen years after approval) warning of the increased risk of stroke or death when used outside of approved indications.[43]

16.4 MANAGING POSTAPPROVAL SAFETY OF DEVICES

There are numerous reasons why it is challenging for regulators to reverse their decisions for approved medical devices, even in the face of mounting evidence that calls a device's safety and effectiveness into question. First is a reluctance to engage in regulatory self-reversal. If devices that the FDA determined to meet statutory criteria are later found to be unsafe or ineffective, it can be uncomfortable for the agency to admit that its previous conclusion is no longer valid. This awkward situation can sometimes be avoided while still protecting patients by narrowing the scope of conditions or populations that fall within the labeled indication. Additionally, revoking approval also risks loss of public confidence in initial approvals, potentially deterring the use of unrelated beneficial treatments. The decision to narrow an indication is an acknowledgement that benefits are no longer believed to exceed risks for certain populations or indications and might logically be expected to lead to similar losses of public confidence, but modified labeling tends to draw less attention and is more likely to be perceived as a refinement rather than a reversal.

Similar psychology is at play with patients and physicians, who may have come to rely on the availability of a new device or who are reluctant to believe that a device that they implanted or that is implanted in them could actually do more harm than good. Research in the social sciences on loss aversion suggests that takebacks can be met with greater resistance than refraining from taking an action (in this case, clearing or approving a device) in the first place.[44] Patients may feel that a potentially beneficial therapy is being withheld from them if it is taken off the market. For physicians, intervention bias in medicine leads to the desire to "do something," even if doing nothing may result in improved clinical outcomes.[45] Physicians may think that they are able to selectively use medical devices in patients who will derive clinical benefit, and professional societies may offer such guidance. However, there are important limitations in patients' and physicians' understanding of regulatory approvals, and they may not recognize that FDA approval still leaves important uncertainty.[46]

[43] US Food & Drug Admin., Use of the Stryker Wingspan Stent System Outside of Approved Indications Leads to an Increased Risk of Stroke or Death: FDA Safety Communication, https://www.fda.gov/medical-devices/medical-device-safety/use-stryker-wingspan-stent-system-outside-approved-indications-leads-increased-risk-stroke-or-death.

[44] Amos Tversky & Daniel Kahneman, Loss Aversion in Riskless Choice: A Reference-Dependent Model*, 106 Quarterly J. Econ. 1039 (1991).

[45] Andrew J. Foy & Edward J. Filippone, The Case for Intervention Bias in the Practice of Medicine, 86 Yale J. Biol. Med. 271 (2013).

[46] Aaron S. Kesselheim et al., Physicians' Knowledge About FDA Approval Standards and Perceptions of the "Breakthrough Therapy" Designation, 315 JAMA 1516 (2016); Tamar Krishnamurti et al.,

To address this challenge, the FDA could publish guidance documents about benchmarks that must be achieved for a medical device to maintain approval after twelve months on the market. For example, the FDA could mandate that a postapproval clinical trial enroll a certain number of patients and meet specific safety and effectiveness endpoints to remain on the market. Devices that do not meet these parameters could then be withdrawn based upon prespecified, published criteria. As medical devices are often modified through PMA supplements,[47] or through the 510(k) pathway,[48] the expectation would be that all new device iterations would also meet these criteria.

A second challenge is that it can be difficult in the postmarket environment to generate high-quality data sufficient to demonstrate that earlier conclusions were wrong. Although randomized controlled trials remain the gold standard for clinical evidence, once a medical device is widely available, regulators rely primarily on observational data. For example, randomized clinical trials of patent foramen ovale occluders studying device ability to reduce the risk of stroke were delayed for several years because there was no incentive to enroll in a randomized trial when the devices were widely available off-trial.[49] Improved analytical tools have emerged to allow more reliable causal inference from observational data, such as propensity score matching,[50] instrumental variable analyses,[51] and the use of falsification hypotheses,[52] but more may be needed. As the granularity of data and the methods of analysis improve, confidence in observational results can be expected to increase.

Third, outcomes may improve as clinicians gain experience with both the device and its associated procedure, as studies show improved outcomes among patients who receive procedures at hospitals with higher versus lower procedural volume.[53] However, because training patients are often excluded from pivotal trial data, the "experience factor" has already been at least partially captured at the time of authorization. Making the data from the training patients available and included in premarket authorization would provide a more accurate assessment of expected

A Randomized Trial Testing US Food and Drug Administration "Breakthrough" Language, 175 JAMA Intern. Med. 1856 (2015).

47 Rome et al., supra note 4.

48 Brent M. Ardaugh et al., The 510(k) Ancestry of a Metal-On-Metal Hip Implant, 368 N. Engl. J. Med. 97 (2013).

49 Patrick T. O'Gara et al., Percutaneous Device Closure of Patent Foramen Ovale for Secondary Stroke Prevention: a Call for Completion of Randomized Clinical Trials: a Science Advisory from the American Heart Association/American Stroke Association and the American College of Cardiology Foundation, 119 Circulation 2743 (2009).

50 Jason S. Haukoos & Roger J. Lewis, The Propensity Score, 314 JAMA 1637 (2015).

51 Matthew L. Maciejewski & M. Alan Brookhart, Using Instrumental Variables to Address Bias from Unobserved Confounders, 321 JAMA 2124 (2019).

52 Vinay Prasad & Anupam B. Jena, Prespecified Falsification End Points: Can They Validate True Observational Associations?, 309 JAMA 241 (2013).

53 Sreekanth Vemulapalli et al., Procedural Volume and Outcomes for Transcatheter Aortic-Valve Replacement, 380 N. Engl. J. Med. 2541 (2019).

initial outcomes in clinical practice,[54] and is necessary to allow patients and clinicians to make adequately informed decisions. Another possibility is for payors to limit reimbursement for certain medical devices to specific hospitals or physicians that have demonstrated expertise and successful outcomes. To protect patients, health systems could implement privileging requirements that require measurable demonstrations of proficiency with such devices, or medical specialty boards could authorize device- or device/procedure-specific certifications. In addition to these private efforts, Congress could expand existing Risk Evaluation and Mitigation Strategies programs to include devices as well as drugs.

A fourth reason is that devices may turn out to be unsafe or ineffective in some clinical circumstances, but still have benefits that outweigh their risks among other indications. For example, coronary stent placement has been shown to improve outcomes in the setting of patients with ST-segment elevation myocardial infarction. However, studies have shown that there is no benefit from coronary stent placement for patients with stable ischemic heart disease.[55] One way to address this scenario is to broaden use of patient decision checklists, such as with the Essure hysteroscopic sterilization device, to ensure that patients are adequately informed of the FDA-approved indications and the current status of data supporting safety and effectiveness prior to providing consent. Informed consent documents could also include clear FDA-required text, for example, that safety and effectiveness have not been demonstrated for particular indications.

Although the FDA formally has the authority to withdraw products when necessary to protect public health, regardless of manufacturer cooperation, it has rarely exercised this power. In one notorious case, the agency withdrew the metastatic breast cancer indication of bevacizumab (Avastin®) after a confirmatory trial failed to show a benefit in overall survival, leaving the drug itself on the market.[56] Even though the withdrawal was in reality only a labeling change, the FDA's decision was extremely unpopular and faced substantial resistance from the manufacturer and public, which led to delays in its implementation despite the recommendation of the FDA's Oncologic Drugs Advisory Panel.[57] CMS even stated that it would continue to cover the drug for the breast cancer indication. Use of bevacizumab

[54] Chen et al. (2011), supra note 4.

[55] David J. Maron et al., Initial Invasive or Conservative Strategy for Stable Coronary Disease, 382 N. Engl. J. Med. 1395 (2020); William E. Boden et al., Optimal Medical Therapy With or Without PCI for Stable Coronary Disease, 356 N. Engl. J. Med. 1503 (2007); Rasha Al-Lamee et al., Percutaneous Coronary Intervention in Stable Angina (ORBITA): a Double-Blind, Randomised Controlled Trial, 391 Lancet 31 (2018).

[56] Julia A. Beaver et al., A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review, 4 JAMA Oncol. 849 (2018); Daniel Carpenter et al., Reputation and Precedent in the Bevacizumab Decision, 365 N. Engl. J. Med. (2011).

[57] Sanket S. Dhruva & Rita F. Redberg, Withdrawing Unsafe Drugs from the Market, 30 Health Aff. (Millwood) 2218 (2011).

decreased,[58] but the experience may have dissuaded the agency from taking similar regulatory actions in the future.

16.5 MANAGING ONGOING POSTAPPROVAL UNCERTAINTY OF EVIDENCE

The FDA's growing enthusiasm for expedited approvals increases the need to rely on postapproval medical device studies to better characterize safety and effectiveness. However, such studies may not be completed in a timely manner (or at all).[59] Noncompletion of postmarket studies within requisite timeframes could also be a basis for revoking FDA approval to better protect public health.

Revoking approval based on lack of study completion is even more challenging than revoking approval based on trial results, since withdrawal for noncompletion of studies necessarily occurs in the absence of required study results and thereby allows hope and belief to override evidence-based practice. If devices are nevertheless withdrawn, patients and physicians may understandably be confused about the meaning of FDA approval: if more evidence was needed to demonstrate safety and effectiveness, then why was the device approved? Once devices are available on the market, generous payments for newer procedures can create a financial incentive for their use. Medical device manufacturers are likely to provide reasonable explanations for why clinical studies have been delayed, such as slow enrolment, and optimistically predict that confirmatory evidence will soon be available. In some cases, manufacturers may have incentives to delay postapproval trials, for example, if concerns remain that confirmatory trials will demonstrate a smaller effect size than in premarket data, or if visible enrolment efforts might engender a perception that a device's benefit is uncertain.[60]

To promote more timely development of evidence for the effectiveness of medical devices after expedited approval, Congress could ensure that devices have their expedited approvals automatically lapse if postapproval clinical trials are not completed or making adequate progress by FDA-imposed deadlines. For example, if a prespecified number of patients are not enrolled into a trial by a certain date, approval would lapse, and future potential patients would need to be enrolled in a clinical trial (as in a preapproval setting). Similarly, the FDA and other stakeholders would need to make clear through public messaging that timely postmarket evidence generation is necessary to prevent lapse of approval of a medical device. There is international precedent for similar regulatory

[58] Rena M. Conti et al., The Impact of Emerging Safety and Effectiveness Evidence on the Use of Physician-Administered Drugs: the Case of Bevacizumab for Breast Cancer, 51 Med. Care 622 (2013).

[59] Rathi et al., supra note 4; Rathi et al., supra note 16; Reynolds et al., supra note 17.

[60] Joseph S. Ross et al., Post-market Clinical Research Conducted by Medical Device Manufacturers: a Cross-Sectional Survey, 8 Med. Devices (Auckl). 241 (2015).

action: in Japan, manufacturers of some devices must refile for approval with updated data from clinicians, clinical trials, and publications after a requisite time period to ensure that the data continue to demonstrate safety and effectiveness of the device.[61] If such a measure is implemented, it will be important to provide clear notice to patients of the limited evidence of benefits and risks to ensure that consent to treatment is truly informed.

[61] Daniel B. Kramer et al., Postmarket Surveillance of Medical Devices: a Comparison of Strategies in the US, EU, Japan, and China, 10 PLoS Med. (2013).