FDA Regulation and Approval of Medical Devices: 1976-2020

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**IMPORTANCE** US law generally requires testing of high-risk medical devices prior to approval, as well as premarket evaluation of moderate-risk medical devices, with the goal of ensuring that the benefits of these products exceed their risks. The US Food and Drug Administration (FDA) attempts to balance the need for evidence generation with an approval process that facilitates access and encourages innovation.

**OBJECTIVE** To review the development of laws and standards affecting the evaluation and oversight of medical devices by the US regulatory system and the outcomes of this system from 1976 to 2020.

**EVIDENCE REVIEW** Laws enacted by US Congress and regulations promulgated by the FDA through 2020; databases maintained by the FDA of device authorizations from 1976 to 2020; and annual reports of user fees paid to the FDA by industry.

**FINDINGS** Since Congress and the FDA initiated premarket review of medical devices in 1976, some fundamental innovations in the device regulation system have included special pathways to accelerate availability of investigational devices, more flexible evidence and review requirements, and increased funding to the FDA through industry-paid user fees. From 1987 to 2020, the annual number of novel devices granted premarket approval (which excludes supplements) ranged from 8 to 56 (median, 32), and the number of clearances for 510(k) devices (those that are “substantially equivalent” to marketed devices) ranged from 2804 to 5762 (median, 3404). User fee funding for devices was established in 2002 and annual fees collected increased from $30 million in 2003 (in 2019 dollars) to more than $208 million in 2019; this represented 43% of FDA funding related to the review of medical devices. Although many new devices have led to considerable patient benefit, such as hypodermic needles and magnetic resonance imaging machines, important adverse events caused by some devices, such as an implanted device for birth control and a surgical mesh implant for pelvic organ prolapse, have led to calls to reexamine the regulatory system for such products.

**CONCLUSIONS AND RELEVANCE** Over the last 45 years, medical device regulation has become more complex, with more regulatory pathways and greater variations in the evidence and controls required for authorization. Increased FDA support from industry and concern about flexible authorization requirements reflect the tension between efficient access and the need for assurances that products will safely benefit patients.

Medical devices occupy a prominent position in health care and among health-related products. According to reports from 2017 and 2018, more than 18,000 manufacturers produce an estimated 190,000 distinct medical devices that are regulated by the US Food and Drug Administration (FDA).\(^1,2\) Spending on medical devices in the US was estimated at $173 billion in 2019,\(^3\) an increase from an estimated $36 billion (in 2019 dollars) in 1983.\(^4\)

The medical device industry is regulated primarily under a framework established by the Medical Device Amendments of 1976\(^6\) to the Food, Drug, and Cosmetic Act of 1938.\(^8\) Because of rapid technological advances over the subsequent 4 decades, the US Congress and FDA modified regulatory standards to minimize unnecessary requirements, promote the availability of innovative devices, adapt to entirely new technologies such as digital mobile apps, and fulfill the agency’s mission as a steward of the public’s health (Box 1). The COVID-19 pandemic has contributed to a renewed focus on the assessment of medical devices and tests, an area of regulation that previously received limited attention.

This Special Communication describes the evolution of laws and standards that have shaped the testing of medical devices, the pathways that exist for FDA authorization, changes in the role and authority of the FDA, trends in the number of devices approved from 1976 to 2020, and the implications for patient care and outcomes.
Sources of evidence included principal federal laws (1906-2020) and FDA regulations and guidance documents (1976-2020); FDA databases of approved or cleared new medical devices (1976-2020); FDA databases of information on postapproval device studies (1991-2020) and Section 522 postapproval studies (2001-2020); and official reports of medical device user fees paid by manufacturers to the FDA (2003-2019).

Methods

Results

The 1976 Risk-Based Classification Framework

In the early 20th century, some manufacturers made fantastic and inadequately supported claims about the curative properties of their medical devices, leading Congress to provide the FDA with authority to take action against mislabeling in 1938, but there was no requirement for premarket review. Acknowledging the need for greater regulation, Congress provided the FDA with premarket review authority in the Medical Device Amendments of 1976, which broadly defined devices to include any “instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article” intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or function of the body, that does not achieve its effect through chemical action.

To promote thorough agency review without creating unnecessary delay, the 1976 legislation created a risk-based classification system that subjected different kinds of devices to graded levels of regulation (Box 2). Low-risk class I devices, such as stethoscopes or elastic bandages, were subject to “general controls,” such as requirements to follow good manufacturing practices and prohibitions against adulteration and misbranding. Moderate-risk class II devices, such as some surgical mesh, ventilators, powered wheelchairs, and joint replacement implants, were subject to additional FDA regulations setting forth performance standards, such as a requirement that a colon capsule endoscopy system can withstand a range of pH values. Many infection-related diagnostic tests or their components are also categorized in class II, such as those for Mycobacterium tuberculosis, dengue virus, and Vibrio cholerae.

High-risk class III devices, such as pacemakers, implantable intraocular lenses, and breast implants, were generally subject to premarket approval application (PMA) requirements involving the submission of full reports of scientific investigations that provided reasonable assurance of safety and effectiveness.

In 1997, the FDA Modernization Act directed the FDA to consider whether such premarket data requirements could be reduced through reliance on postmarket controls such as surveillance during clinical use. The law also introduced a requirement that the FDA inform applicants of the “least burdensome” means of establishing effectiveness for PMAs or substantial equivalence for 510(k) submissions.

Premarket Approval

The FDA’s premarket approval of devices must be based on valid scientific evidence, but clinical trial data are required only “where appropriate.” Evidence may be derived from well-controlled investigations, partially controlled studies, studies without matched controls, well-documented case histories, or the open-ended category of “reports of significant human experience.” The term approval is applied to devices authorized via the PMA pathway, while clearance indicates the device has been authorized via the 510(k) pathway.

The 510(k) Pathway

New devices often comprise modifications of existing products, such as an altered testing protocol for an in vitro diagnostic or a new shape or different materials for an intravascular stent. Changes to approved PMAs can occur via PMA supplements (including, eg, panel-track supplements, which are submitted when substantial clinical data are needed to support a significant change to a device). Devices introduced after 1976 are generally designated as class III and require a PMA unless the manufacturer can demonstrate that the device is “substantially equivalent” to a previously marketed “predicate” device, in which case the new or modified device will be classified according to the class of its predicate. To request a substantial equivalence determination for any class of device not subject to a PMA requirement, a manufacturer has to notify the FDA at least 90 days in advance of proposed marketing by preparing a submission referred to as a 510(k), after the section of the Food, Drug, and Cosmetic Act in which it is found, which requires documentation of similarity in characteristics such as materials, design, energy usage, or operational principles. Performance data could help support these determinations.

Modified 510(k) Pathways

Created in 1998, the Abbreviated 510(k) Program allows manufacturers to establish “substantial equivalence” and provide a reasonable assurance of safety and effectiveness by submitting summary reports that briefly describe the testing performed, declaring conformance with FDA-recognized consensus standards, or through reliance on other special controls, and were expected to require less data than traditional 510(k)s. As of October 2020, the FDA listed 1430 recognized consensus standards, including those relating to suture diameter, optical properties of contact lenses, and wheelchair test methods.

To facilitate certain modifications to a manufacturer’s own device, such as changes to the labeled indication not requiring new clinical or animal data, the FDA in 1998 established the Special 510(k)
Box 1. Landmark Legislation Relating to Medical Devices, With Selected Provisions

**Federal Food, Drug, and Cosmetic Act of 1938**
Prohibited the marketing of medical devices prepared in unsanitary conditions or bearing false or misleading labeling.

**Radiation Control for Health and Safety Act of 1968**
Authorized the Secretary of Health, Education, and Welfare (the predecessor to the Department of Health and Human Services, within which the FDA is situated) to establish performance standards to control the emission of radiation from a broad range of products, including medical devices such as diagnostic X-ray equipment.

**Medical Device Amendments of 1976**
Provided the FDA with comprehensive authority to regulate medical devices, including the establishment of the premarket approval and 510(k) pathways and the risk-based classification of medical devices into classes I, II, and III.

**Safe Medical Devices Act of 1990**
Increased postmarket reporting and surveillance requirements, including Section 522 studies, and created the Humanitarian Device Exemption for devices addressing a disease or condition affecting fewer than 4000 (now 8000) people in the US per year.

**FDA Modernization Act of 1997**
Exempted most class I devices from premarket notification, created the Third-Party Review Program for 510(k) submissions, authorized expanded access to investigational devices, and required the FDA to inform applicants of the “least burdensome” means of establishing effectiveness for premarket approvals or substantial equivalence for 510(k) submissions.

**Medical Device User Fee and Modernization Act of 2002**
Established a user fee program by which medical device manufacturers pay fees that help fund FDA review activities and provided definitions of panel-track supplements, 180-day supplements, real-time supplements, and efficacy supplements.

**FDA Amendments Act of 2007**
Reauthorized device user fees and directed the FDA to require unique device identifiers.

**FDA Safety and Innovation Act of 2012**
Reauthorized device user fees, eliminated the requirement to first submit a 510(k) prior to eligibility for de novo review, and directed the FDA to include devices in its postmarket risk identification system (Sentinel).

**21st Century Cures Act of 2016**
Established the Breakthrough Devices Program, excluded most clinical decision support software from the definition of medical device, and raised the Humanitarian Device Exemption limit from 4000 to 8000.

**FDA Reauthorization Act of 2017**
Reauthorized device user fees and authorized risk-based inspection scheduling for device manufacturers.

FDA indicates Food and Drug Administration.

Program, which allowed the FDA to rely in part on previous reviews. In 2018, citing the “least burdensome” provisions, the FDA announced the creation of the Safety and Performance-Based Pathway, which focused on performance-based criteria, such as tensile strength or durability, instead of direct comparative testing against a predicate device.

A 1997 Accredited Persons Program permitted manufacturers to submit 510(k)s related to most class I and nonimplantable, nonlife-sustaining class II devices to third parties that make recommendations to the FDA on substantial equivalence. To improve quality of third-party reviews and avoid routine agency re-review, the FDA in 2017 committed to conducting audits and providing retraining when necessary. As of 2021, 10 third-party reviewers were accredited, including the New York State Department of Health and several small review companies including BeanStock Ventures.

**Exempt Devices**
Following the 1976 Amendments, the FDA exempted many class I devices from 510(k) notification, including patient scales, elastic bandages, and examination gloves. The FDA’s authority was broadened in 1997 to allow it to exempt class II devices without first downclassifying them to class I, if not necessary to provide reasonable assurance of safety and effectiveness, and the agency began applying this approach to exempt devices such as mercury thermometers, adjustable hospital beds, and suction devices.

For devices not specifically exempted, changes not expected to affect the intended use, safety, or effectiveness of a device may not require a 510(k) submission; manufacturers can conduct a risk-based assessment and approve changes themselves, in compliance with the FDA’s Quality System regulation. Manufacturers may also be able to strengthen labeling warnings prior to the FDA’s approval of a PMA supplement by notifying the FDA of the changes being effected.

**De Novo Pathway**
The 1976 Amendments allowed manufacturers to petition the FDA for initial classification as class I or II, but the process required advisory panel review. In 1997, this process was streamlined into the “de novo” classification pathway but could occur only after 510(k) submission and a finding of not substantially equivalent. In 2012, Congress further simplified the procedure by removing the requirement to first submit a 510(k).

**Precertification Digital Products**
The digital revolution of the late 20th century increased the centrality of software to medical devices. In 1987, the FDA issued the first of a series of key policy documents acknowledging that software affecting diagnosis or treatment could meet the definition of a medical device. Modern examples include software that allows a smartphone to view magnetic resonance images for diagnostic purposes or helps detect breast cancer.

Free-standing software would be classified based on risk, while software in a medical device was subject to regulation based on the classification of its parent device. Among the relevant risks were issues of operational quality, reliability, and security vulnerabilities, such as computer hacking or viruses. Most clinical decision support software, intended to guide clinicians with diagnosis and treatment, was excluded from the definition of a medical device by the 21st Century Cures Act of 2016.

Recognizing the iterative nature of software, the FDA in 2017 announced the Software Precertification (PreCert) Pilot Program, intended to evaluate whether software companies with a demon-
stated “culture of quality” could market certain types of digital health products without FDA review or after a shortened review.59

Expanded Access
Because the FDA does not regulate the practice of medicine, approved devices may be used off-label.59 In 1985, the FDA stated it would exercise “enforcement discretion” to allow single-patient emergency use of unapproved medical devices in life-threatening circumstances, with later justification provided by the physician to the FDA. For example, an unapproved artificial heart might be urgently needed. This approach was broadened in 1997 to authorize nonemergency, prospectively planned access by 1 or more patients with immediately life-threatening or serious conditions,51 closely paralleling the FDA’s 1987 policy on expanded access to medications.52 The average annual number of requests for such prospectively planned access to devices was 369 from 2014 to 2019, with more than 99% approved and no apparent trend over time.53,54

Humanitarian Device Exemption
The Safe Medical Devices Act of 1990 created the Humanitarian Device Exemption, which exempted Humanitarian Use Devices, such as a right ventricular assist device and inserts for the treatment of keratoconus from the usual effectiveness requirement when intended to treat rare diseases affecting fewer than 4000 people in the US per year (increased to 8000 people per year in 2016). Such devices were required to demonstrate the absence of unreasonable or significant risk and that probable benefit, generally based on nonclinical evidence,55 outweighed the risk of injury from use.56 These devices could originally be sold for no more than the cost of development, production, and distribution,57 but in 2007, Congress enacted a broad exception allowing for-profit sales based on the number of devices needed to treat up to 4000 (now 8000) patients.58

The Humanitarian Device Exemption requires approval by an institutional review board,59 and in 1992, the FDA proposed to treat such devices as experimental.60 However, in 1996, the agency determined that the exemption should be treated as a temporary premarket approval, so research informed consent is not required.56 Under the 1990 law, a Humanitarian Device Exemption expired after 18 months unless extended by the FDA, but this limitation was removed in 1997, effectively making the approval permanent. From 1990 to 2020, the FDA approved 76 exemptions for humanitarian devices, several of which have been withdrawn or superseded by 510(k)s or PMAs.61 The total number of such approvals was 28 from 1997 to 2002, 20 from 2003 to 2008, 14 from 2009 to 2014, and 14 from 2015 to 2020.

Breakthrough Devices
The FDA Modernization Act of 1997 directed the FDA to provide “review priority” for PMA devices that represented breakthrough technologies or for which no approved alternatives existed, meaning that the application would be given priority in the review queue and receive additional FDA resources.62 Of 230 devices approved from 2005 to 2015, 201 (87%) received standard review and were approved in a median of 14 months, whereas the 29 devices (13%) that received expedited review were approved in a median of 21 months,63 likely reflecting the FDA’s practice of referring most expedited PMAs to an advisory committee.64

Box 2. Device Classes and Approval Pathways (Year Established)

<table>
<thead>
<tr>
<th>Classes (1976)</th>
<th>Pathways or Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I. Low-risk devices for which “general controls” (eg, good manufacturing practices) are sufficient</td>
<td>Exempt (1976). The FDA is authorized to exempt devices from premarket notification (510(k)) and other requirements of the Device Amendments of 1976. Following amendments in 1997, most class I devices are exempt.</td>
</tr>
<tr>
<td>Class II. Moderate-risk devices for which “special controls” (eg, performance standards) are required</td>
<td>510(k) (1976). Devices that are “substantially equivalent” to marketed devices may be marketed following notification to the FDA at least 90 days in advance of commercial distribution. Most class II devices require 510(k) submissions.</td>
</tr>
<tr>
<td>Class III. High-risk devices that generally require premarket approval</td>
<td>Premarket approval (1976). High-risk devices require the submission of full reports of scientific investigations that provide reasonable assurance of safety and effectiveness. Class III devices generally require premarket approval.</td>
</tr>
<tr>
<td>Humanitarian Device Exemption (1990). Devices may be exempt from the usual effectiveness requirement if they are intended to benefit patients with rare diseases, ie, those affecting fewer than 8000 people per year.</td>
<td>Special 510(k) (1998). A manufacturer may establish substantial equivalent by submitting summary reports showing that a device meets performance criteria described in FDA guidance documents or FDA-recognized consensus standards.</td>
</tr>
<tr>
<td>Accelerated Device Approval Services and SGS North America) that make recommendations to the FDA on substantial equivalence.</td>
<td>Special 510(k) (1998). A manufacturer may rely on previous agency review of information when making changes to its own previously marketed device.</td>
</tr>
<tr>
<td>Abbreviated 510(k) (1998). A manufacturer may establish substantial equivalence by submitting summary reports showing that a device meets performance criteria described in FDA guidance documents or FDA-recognized consensus standards.</td>
<td>Supplements (panel-track, 180-day, real-time, efficacy) (2002). A manufacturer wanting to alter a device may submit a supplement to an approved premarket approval application.</td>
</tr>
<tr>
<td>Special 510(k) (2002), but legislation in that year codified the definitions of the various supplement types, including panel-track supplements (which are submitted when substantial clinical data are needed to support a significant change to a device).</td>
<td>Supplements in use prior to 2002, but legislation in that year codified the definitions of the various supplement types, including panel-track supplements (which are submitted when substantial clinical data are needed to support a significant change to a device).</td>
</tr>
<tr>
<td>Breakthrough Devices (2016). Devices providing more effective treatment for life-threatening or irreversibly debilitating conditions may be designated as Breakthrough Devices and receive expedited testing and priority review.</td>
<td>Preshipment Review (2007). Software companies with a demonstrated “culture of quality” can market certain types of digital health products without FDA review or after a shortened review.</td>
</tr>
</tbody>
</table>

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Figure 1. Number of Premarket Approvals, De Novo Reviews, and Panel-Track Supplements, 1976-2020

![Graph showing the number of approvals for different time periods.](https://jamanetwork.com/)

Source: Adapted from Food and Drug Administration (FDA) downloadable premarket approval files. The Medical Device Amendments of 1976 established the premarket approval pathway for high-risk devices. De novo review is a pathway described in the FDA Modernization Act of 1997 and is used to authorize lower-risk (class I or II) devices that lack predicates. A panel-track supplement is a supplement to an approved premarket application that requests a significant change in design or performance of the device, or a new indication for use of the device, and for which clinical data are generally necessary to provide a reasonable assurance of safety and effectiveness. The term panel-track supplement was defined in the Medical Device User Fee Modernization Act of 2002, but FDA regulations previously described certain supplements as “panel-track supplements” and the FDA downloadable premarket approval files categorize these as “panel-track supplements” beginning in 1987.

In 2011, the FDA’s Center for Devices and Radiological Health, acting within its existing authorities, piloted an Innovation Pathway to expedite development and review of breakthrough technologies, which evolved into the voluntary Expedited Access Pathway in 2015. The following year, the 21st Century Cures Act created a more comprehensive Breakthrough Devices Program that offered both expedited testing and priority review for devices providing more effective treatment for life-threatening or irreversibly debilitating conditions. A Breakthrough Device designation can be granted early in the development cycle based on preliminary bench or animal data and applies to the 510(k), PMA, and de novo pathways. The program encourages flexible trial design, use of postmarket data collection, and involvement of senior agency personnel.

User Fees

In 1992, Congress adopted the Prescription Drug User Fee Act to provide funding and targeted timelines to speed FDA review of new drugs. Building on this example, Congress in 2002 enacted the Medical Device User Fee and Modernization Act (MDUFA), which authorized the FDA to collect user fees from device makers to enhance the FDA’s capacity for more timely authorization of new devices. MDUFA funding facilitated activities such as the development of guidance and regulations, preapproval inspection of manufacturing facilities, and evaluation of postmarket studies required as a condition of approval. In 2019, user fees accounted for approximately 43% of the FDA’s device review budget.

As with the Prescription Drug User Fee Act, the FDA negotiated commitment letters with industry under MDUFA and its reauthorization phasing in and gradually reducing review time targets. For example, by 2022, the FDA aims to issue an initial decision for 90% of PMA submissions within 180 calendar days from receipt, excluding days waiting for information from the applicant (“FDA days”), or within 320 days if advisory committee input is required; 70% of de novo submissions within 150 FDA days; and 95% of 510(k) devices within 90 FDA days.

Number of Devices and Pathways

The FDA has approved or cleared more than 155,000 new devices since 1976. Approximately 99% used the 510(k) pathway: between 2015 and 2020, the mean number of PMAs approved annually was 38 PMAs, compared with a mean of 2982 510(k)s per year (and a mean of 22 panel-track supplements per year), with no apparent long-term trends (Figure 1 and Figure 2). Use of the de novo program increased following the amendments in 2012 that eliminated the requirement to first submit a 510(k), which a median of 26 de novo devices was approved annually from 2013 to 2020. Of 77 cardiac implantable electronic devices granted PMA from 1979 to 2012, a median of 50 supplements was associated with each.

Most 510(k)s do not use the Special or Abbreviated review programs and use of the Third-Party Review Program has declined from a peak of 9.3% in 2008 to 2.4% in 2020. Poor-quality third-party review has been cited as the cause of routine FDA re-review of submissions, possibly contributing to low use of the Third-Party Review Program (Figure 2). In 2012, the FDA Safety and Innovation Act required the FDA to reaccredit third parties every 3 years, increasing its ability to ensure quality.
The number of Breakthrough Device Designations has increased annually: 11 in 2016, 19 in 2017, 55 in 2018, 74 and 138 in 2019. Of the first 100 Breakthrough Device Designation requests, 71 were granted. At least 23 such devices have been authorized for marketing, including software intended to detect diabetic retinopathy by analyzing images of the eye (de novo pathway), a blood test to help diagnose traumatic brain injury (de novo pathway), and an implantable endobronchial valve for treating severe emphysema (PMA).

Approval Speed
The average time from submission to PMA approval has varied from about 300 days to 1000 days. The average time to 510(k) clearance has generally remained less than about 200 days (Figure 3).

Evidence Supporting New Devices
An evaluation of 123 studies included in 78 PMAs for cardiovascular device approval from 2000 to 2007 found that 33 (27% of 123) were randomized and 17 (14%) were blinded; 51 approvals (65% of 78) were based on a single clinical trial. Of 213 end points, 187 (88%) were surrogate measures, such as target lesion revascularization for a coronary stent and lead implant success for an electrophysiology device, which are believed likely to correlate with clinical outcomes. Studies in other therapeutic areas have found similar weaknesses in trial design. By contrast, in applications for medication approvals from 2005 to 2012, a comparable study of 448 pivotal trials of 188 drugs for 201 indications found that 400 (89% of 448) were randomized, 356 (80%) were double-blind, and 219 (49%) were based on surrogate measures. Of the 201 approved indications, 74 (37%) were based on a single pivotal trial.

A review of 83 clinical studies that supported 78 panel-track supplements from 2006 to 2015 found 71 (91%) of the supplements were supported by a single study, 37 (45%) of the studies were randomized and 25 (30%) were blinded, and 121 (81%) of 150 primary end points were surrogates. The FDA reported that it requests clinical data for less than 10% of 510(k) submissions. More than 75% of 510(k) device submissions were determined to be substantially equivalent to existing products, while less than 5% were not substantially equivalent (the remainder being withdrawn, exempt, or having another disposition).

Figure 2. Food and Drug Administration’s (FDA) 510(k) Decisions, 1976-2020

<table>
<thead>
<tr>
<th>Year</th>
<th>Clearances (n)</th>
<th>Median (IQR) annual clearances by 10-y time periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976-1985</td>
<td>3073 (2194-3526)</td>
<td>3073 (2194-3526)</td>
</tr>
<tr>
<td>1986-1995</td>
<td>4323 (4184-4953)</td>
<td>4323 (4184-4953)</td>
</tr>
<tr>
<td>1996-2000</td>
<td>3532 (3004-3122)</td>
<td>3532 (3004-3122)</td>
</tr>
<tr>
<td>2001-2005</td>
<td>3043 (3004-3122)</td>
<td>3043 (3004-3122)</td>
</tr>
<tr>
<td>2006-2010</td>
<td>2929 (2898-3013)</td>
<td>2929 (2898-3013)</td>
</tr>
</tbody>
</table>

Source: Adapted from FDA downloadable 510(k) files. The Medical Device Amendments of 1976 established the 510(k) pathway, which authorizes the FDA to clear devices for marketing based on substantial equivalence to a predicate device. The FDA created the Special and Abbreviated 510(k) review programs in 1998. The Special 510(k) Program allows a manufacturer to obtain clearance of modifications to its own previously marketed device based on summary information in cases where the change does not affect the intended use or alter the device’s fundamental scientific technology. The Abbreviated 510(k) Program allows manufacturers to establish substantial equivalence to a predicate device by showing that a device meets performance criteria described in FDA guidance documents, FDA-recognized consensus standards, or special controls. The FDA Modernization Act of 1997 created the Third-Party Review Program, which permits manufacturers to submit 510(k)s related to most class I and nonimplantable, nonlife-sustaining class II devices to third parties, for a fee, which then make recommendations to the FDA on substantial equivalence.

a Third-party review is not included in the stacked bar graph because it is not mutually exclusive with the other 3 categories.

b Prior to 1998, 100% of clearances occurred via the Traditional 510(k) pathway.
Experience [MAUDE], 1995),24 and generate higher-quality adverse event reports (Manufacturer and User Facility Device Reporting, 1976 Amendments, but were limited in scope.94 In 2007, reporting requirements were strengthened in the Safe Medical Devices Act of 1990, and a series of initiatives were under-

Despite FDA efforts to encourage reporting through its voluntary training or experience, and require reports from manufacturers and distributors about postmarket safety and effectiveness. Because of the inherent limits of fully defining a product’s reliability, risks, and effectiveness based on preapproval data, the FDA can require postapproval studies at the time of PMA approval.98,99 To complement these postapproval studies, the Safe Medical Devices Act of 1990 directed the FDA to require mandatory postmarket surveillance (Section 522 studies) for certain permanently implanted, life-sustaining, or high-risk devices,100 but Congress removed this requirement and made it discretionary on the part of the FDA in 1997.

Of 193 PMAs and 20 Humanitarian Use Devices approved between 2005 and 2011, postapproval studies were required for 93 (48%) and 10 (50%), respectively.101 The most common study type is the prospective cohort study (type I or II),100 with the greatest proportion being included in various congressional enactments beginning with the 1976 Amendments, but were limited in scope.94 In 2007, Congress ordered the FDA to more comprehensively require unique device identifiers (UDIs) unless granted an exception by the FDA, and the agency promulgated regulations phasing in UDI requirements by 2020 (an “enforcement discretion” policy deferred compliance for certain class I and unclassified devices and existing devices held in inventory96). However, the FDA has no authority to mandate inclusion of UDIs in electronic health records.96 and health systems have not yet voluntarily done so, limiting their usefulness.97

User Fees
In 2020, MDUFA fees were $340 995 per PMA, $255 747 per panel-track supplement, $102 299 per de novo request, and $11 594 per 510(k),89 with certain waivers or reductions available. Total device user fees collected increased from $30 million in 2003 (in 2019 dollars) to more than $208 million in 2019, or approximately 43% of the $483 million in funding related to the review of medical devices.90

General Postmarket Surveillance
The Medical Device Amendments of 1976 authorized the FDA to impose postmarketing restrictions on the sale or distribution of devices, limit their use to certain facilities or people with specific training or experience, and require reports from manufacturers and distributors about postmarket safety and effectiveness. Despite FDA efforts to encourage reporting through its voluntary Device Experience Network,91 most events went unreported.92 Reporting requirements were strengthened in the Safe Medical Devices Act of 1990, and a series of initiatives were under-

taken to simplify physician reporting (MedWatch, 1993),93 store adverse event reports (Manufacturer and User Facility Device Experience [MAUDE], 1995),74 and generate higher-quality reports from certain medical facilities (Medical Product Safety Network [MedSun], 2002).

Identification systems to assist with postmarket device tracking were included in various congressional enactments beginning with the 1976 Amendments, but were limited in scope.74 In 2007, the FDA defined less than half (47%) of the 792 postapproval studies it had ordered since 1991 as “completed,” with another 31% as “progress adequate.” A review of 33 postapproval studies

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**Figure 3. Mean Number of Days From Food and Drug Administration (FDA) Receipt of Submission to FDA Decision**

<table>
<thead>
<tr>
<th>Device category</th>
<th>Mean days by time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarket approval</td>
<td>483</td>
</tr>
<tr>
<td>510(k)</td>
<td>53</td>
</tr>
<tr>
<td>De novo</td>
<td>356a</td>
</tr>
</tbody>
</table>

Source: Adapted from FDA downloadable premarket approval and 510(k) data files. The Medical Device Amendments of 1976 established the premarket approval pathway, for high-risk devices, and the 510(k) pathway, which authorizes the FDA to clear devices for marketing based on substantial equivalence to a predicate device. De novo review is a pathway described in the FDA Modernization Act of 1997 and used to authorize lower-risk (class I or II) devices that lack predicates. The FDA explained that the peak in 1993-1994 for 510(k)s was a result of several factors, including its exempting of many low-risk devices from 510(k) review, which resulted in remaining devices being more complex on average, and the removal of the exemption for patient examination gloves in the context of the AIDS/HIV epidemic, which resulted in a surge of more than 1500 additional 510(k) submissions in 1989.98 However, these 2 explanations are in some tension with one another and fail to explain the near-simultaneous peak in premarket approval times. No clear trend is present following the enactment of the Medical Device User Fee and Modernization Act in 2002.

a Data are from 2013 to 2020. Because Congress eliminated the need to first submit a 510(k) in 2012, comparable time-to-clearance data for pre-2013 de novo submissions are not available.
ordered from 2010 to 2011 found 6 (18%) had been completed by 2014.81 Section 522 studies can take various forms, most commonly a cross-sectional study (Table). Between 2001 and 2020, 399 such studies were mandated.102

### Discussion

Legislation since 1976 has followed a risk-based framework for device regulation in which the amount of clinical data required and the standards of FDA review increase with the complexity of the device or its risk to patient health. Such tiered regulation allows the FDA to devote more time and resources to higher-risk products, which are also subject to a higher evidentiary standard than lower-risk products, allowing more efficient allocation of regulatory resources. It also permits more rapid adoption of incremental changes intended to improve medical devices for the benefit of patients when the changes are considered to involve little risk.

As with drugs, delays and costs imposed by these protective regulations have created pressure for Congress to reduce premarket requirements, such as by shifting some data collection to the postmarket period. Some new devices no longer require premarket approval under the de novo pathway, evidence requirements have been streamlined through the Special and Abbreviated

### Table. Postapprovala and Section 522b Medical Device Studies

<table>
<thead>
<tr>
<th>Study type</th>
<th>No. (%)</th>
<th>Study type</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postapproval studies, 1991-2020 (n = 792)</td>
<td>Section 522 studies, 2001-2020 (n = 399)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 187</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>527 (67)</td>
<td>42 (22)</td>
<td></td>
</tr>
<tr>
<td>Randomized clinical trial</td>
<td>54 (7)</td>
<td>8 (4)</td>
<td></td>
</tr>
<tr>
<td>Bench/laboratory study</td>
<td>32 (4)</td>
<td>30 (16)</td>
<td></td>
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<tr>
<td>Active surveillance</td>
<td>33 (4)</td>
<td>0</td>
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</tr>
<tr>
<td>Pro-/retrospective study</td>
<td>35 (4)</td>
<td>4 (2)</td>
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</tr>
<tr>
<td>Cross-sectional</td>
<td>11 (1)</td>
<td>86 (46)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>100 (13)</td>
<td>18 (10)</td>
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</tr>
<tr>
<td>Status as of April 11, 2021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>374 (47)</td>
<td>32 (8)</td>
<td></td>
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<tr>
<td>Progress adequate</td>
<td>242 (31)</td>
<td>16 (4)</td>
<td></td>
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<tr>
<td>Terminated</td>
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<td>97 (25)</td>
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<tr>
<td>Study pending</td>
<td>30 (4)</td>
<td>7 (2)</td>
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<tr>
<td>Progress inadequate</td>
<td>27 (3)</td>
<td>5 (1)</td>
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<tr>
<td>Consolidated</td>
<td>0</td>
<td>107 (27)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>61 (8)</td>
<td>135 (34)</td>
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</tr>
</tbody>
</table>

Source: Adapted from the Food and Drug Administration (FDA).

a The FDA interpreted the Medical Device Amendments of 1976 to provide the authority for imposing postapproval requirements at the time of premarket approval.89

b The Safe Medical Devices Act of 1990 directed the FDA to require mandatory postmarket surveillance (Section 522 studies) for certain high-risk devices, a requirement that was made discretionary on the part of the FDA in 1997.

c Totals may not add to 100% due to rounding.

d A prospective cohort is one in which the participants in a defined population are followed. A randomized clinical trial compares the effects of 1 or more interventions against a control group, and participants are assigned randomly to 1 of the study groups. A bench/laboratory study involves bench testing, such as wear or fatigue testing of a device. Active surveillance involves monitoring of the distribution and trends in the incidence of adverse events through ongoing, active systematic collection, analysis, and interpretation of data. A pro-/retrospective study is a hybrid cohort study in which data are collected both retrospectively and prospectively. A cross-sectional study assesses the presence or absence of an exposure and health outcome at the same point in time.100 Consolidated means that 2 or more Section 522 study orders were consolidated into a single order. "Other" includes, for example, a manufacturer that has ceased marketing the product subject to the study requirement.

e Data exclude 210 studies for which the study type field was empty, indicating, for example, that the manufacturer had ceased distribution or revised the indication to no longer include an indication that had been the subject of the Section 522 order.

f Includes comprehensive/linked/registry-based surveillance (n = 33, 4%), enhanced surveillance (n = 16, 2%), not specified (blank) (n = 16, 2%), retrospective cohort study (n = 11, 1%), case-control study (n = 5, 1%), meta-analysis (n = 2, <1%), animal study (n = 1, <1%), and other (n = 16, 2%).

f Includes retrospective cohort study (n = 6, 3%), enhanced surveillance (n = 3, 2%), case-control study (n = 1, 1%), and other (n = 8, 4%).

h Includes revised/replaced study (n = 24, 3%), protocol pending (n = 10, 1%), protocol overdue (n = 1, <1%), and other (n = 26, 3%).

i "Other" includes revised/replaced study (n = 6, 2%), not specified (blank) (n = 2, 1%), noncompliant (n = 2, 1%), plan pending (n = 1, <1%), and other (n = 124, 31%).
510(k) Programs and the Breakthrough Devices Designation, and the Humanitarian Device Exemption means that patients with rare diseases cannot be reasonably assured that their devices actually improve their condition. Even when evidence requirements remain unchanged, patients may be using products before that evidence has been gathered via the Expanded Access Program.

The overall effects of efforts to streamline review and lower development costs are unclear. The number of PMA approvals has exhibited no definite trend since the 1990s. 510(k) clearances are numerous and appear to have stabilized at around 3000 per year since 2007. The number of de novo applications and panel-track supplements has increased, but only a few dozen of these are authorized each year. The Breakthrough Devices Program has become more frequently used, but authorizations of devices bearing this designation are not yet numerous and such designations may be made without either clinical or animal data, creating uncertainty as to patient benefit. Approval speed of PMAs has exhibited no obvious trends and 510(k) approvals have become slower.

Concerns have been raised that clinical outcome data are generated and submitted for only a small fraction of medical devices. Even when a PMA is required, evidence requirements for device approval tend to be highly flexible. For example, device approval requires clinical data only “where appropriate,” and the FDA can accept other “valid scientific evidence” in lieu of investigations when evaluating device effectiveness. Average total costs to bring a device from concept through PMA or 510(k) clearance were estimated in 2010 to be $94 million and $31 million, respectively, compared with estimates of hundreds of millions or more for approval of new drugs, likely reflecting devices’ shorter development timelines and reduced clinical data requirements.

The 510(k) process has been controversial because it allows changes to be implemented with limited testing if a new device is considered substantially equivalent to a predicate device, but many predicate devices have never been formally evaluated by the FDA for safety and effectiveness. A 1983 congressional report warned that if a predicate device “poses risks, or lacks efficacy, so also will the new [510(k)-cleared] device pose risks or lack efficacy,” and expressed concern that the 510(k) process had become a more permissive regulatory tool than Congress had envisioned. Despite this early recognition by policy makers, it remains unclear whether the medical community (or patients) was widely aware of these limitations.

The absence of efficacy or undetected presence of harm in predicate devices are not the only concerns. In some cases, substitutions thought to be substantially equivalent may yield unanticipated consequences. For example, the use of cobalt-chromium alloy instead of ceramic-polyethylene in hip replacement devices, which had been permitted as substantially equivalent under the 510(k) program, was associated with a greater need for surgical revision by year 7 (6.3% vs 3.7%). In 2016, the FDA ordered manufacturers of metal-on-metal hip implants to file PMAs or face market removal. Similar concerns have arisen with PMA supplements. For example, changes to the width and welding techniques of leads or alternative interventions. For example, more than 5000 adverse event reports were recorded in the 13 years following the 2002 approval of an implanted sterilization device (Essure).

By the time evidence is generated and appropriate disclosures are made, the market may have moved on to future product iterations or alternative interventions. For example, more than 5000 adverse event reports were recorded in the 13 years following the 2002 approval of an implanted sterilization device (Essure). Responding to concerns, the FDA issued a draft disclosure document in 2016 and restricted distribution to ensure disclosure to patients in 2018, but the manufacturer announced the device’s voluntary removal.118 Similar concerns have arisen with PMA supplements. For example, changes to the width and welding techniques of leads or alternative interventions. For example, more than 5000 adverse event reports were recorded in the 13 years following the 2002 approval of an implanted sterilization device (Essure). Responding to concerns, the FDA issued a draft disclosure document in 2016 and restricted distribution to ensure disclosure to patients in 2018, but the manufacturer announced the device’s voluntary removal.

In a 2011 report, the Institute of Medicine recommended that the 510(k) process and its substantial equivalence standard be replaced with an integrated pre- and postmarket regulatory framework that provided better assurance of safety and effectiveness. Following the report, the FDA issued new guidance documents and held a public meeting to address what device modifications required 510(k)s, but Congress has not yet implemented the recommended changes. In 2012, the FDA also began to develop a system that evolved into the National Evaluation System for Health Technology, which seeks to leverage data from clinical settings to clarify benefits and risks and generate evidence to support new uses of devices. In 2016, Congress directed the FDA to further increase the emphasis on real-world evidence to help support new indications or satisfy postmarket study requirements, and the FDA issued guidance carrying out this directive the following year.

As with the evolving framework for regulating drugs, developments in device regulation have increasingly shifted much evidence collection from the pre- to postmarketing period. The Safe Medical Devices Act authorized postapproval surveillance or patient registries in lieu of performance standards, even though patients and clinicians likely rely on the fact of FDA authorization to indicate that a product has already been determined to be safe and effective. The requirement that manufacturers phase in UDIs by 2020 was designed to, among other purposes, enhance the capacity for postapproval surveillance of device safety (and potentially comparative effectiveness studies as well) using data from clinical settings, as the device numbers are analogous to the National Drug Code numbers assigned to each marketed drug, which specifically identify each dose and manufacturer. One intended goal was for UDIs to enable more rapid identification of the outcomes associated with each use of a device, similar to the approach used to track the safety and other outcomes of medications. UDIs could also facilitate studying utilization patterns and contacting patients in the event of a product warning or recall. However, health care organizations and insurers have not yet adequately integrated patient-level UDI information into their payment and data streams, limiting the utility of UDIs for these purposes and calling into question the practicality of replacing premarket review with comprehensive postmarket surveillance.

In a market characterized by the rapid introduction of modifications and new devices, postapproval studies can face enrollment challenges and generally take several years to complete, potentially exposing large numbers of patients to a device without appropriate disclosure. For example, a 2015 study of 92,000 women found that about 1 in 11 who received 510(k)-cleared surgical mesh implants to treat pelvic organ prolapse experienced problems, a risk that would have been detectable with a smaller number of patients studied systematically prior to authorization.

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removal from the market just 3 months later, citing “decreased use of permanent contraception” among US women in favor of “other birth control options.” An estimated 750,000 women were exposed to the device before its withdrawal.29

In some cases, postapproval information may never be systematically collected, such as when a device manufacturer requests that the FDA remove an indication so that a Section 522 study does not need to be completed. For example, a vaginal prolapse repair indication was removed from a surgical mesh device (Obtryx System; Boston Scientific), which was also indicated for treatment of urinary incontinence.

As FDA regulation increasingly relies on evidence obtained from patients in the postmarket environment, there becomes a greater need to ensure informed patient consent for use of these devices. Unlike drugs, many devices are not obtained from pharmacies, and patients are therefore unlikely to be provided with product labeling, increasing the burden on physicians to properly communicate product benefits and risks. The lack of device analogues to state generic drug substitution laws means that the influence of physician product choice on patient financial obligations is likely to be greater, on average, than it is for drugs. Use of new devices based on limited evidence can potentially displace proven technologies with longer safety records. Most critically, reliance on data from clinical settings in markets with short life cycles and rapid obsolescence raises questions about the regulatory system’s ability to protect patients from devices that are unsafe or less effective than preapproval evidence suggests.

Increased user fee funding has allowed the FDA to devote greater resources to device regulation and approval, but may also affect the attitudes of agency personnel toward congressional legislation and other matters. New programs may help reduce industry costs and suggest theoretical savings to patients, but the increasing complexity of medical device regulation can be justified only to the extent it benefits patient health or financial circumstances. Not enough is known about the extent to which new devices outperform older ones, or whether differences in performance are justified by differences in cost, making it difficult to assess the value of special authorization pathways. Achieving the proper balance between development costs and willingness of industry to introduce new devices cannot be determined without knowledge of the magnitude of incremental benefits that new devices offer.

Conclusions

Over the last 45 years, medical device regulation has become more complex, with more regulatory pathways and greater variations in the evidence and controls required for authorization. Increased FDA support from industry and concern about flexible authorization requirements have created tension between efficient access and assurances that products will safely benefit patients.

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REFERENCES


55. US Food and Drug Administration. Humanitarian Device Exemption (HDE) program.