The US Food and Drug Administration (FDA) is among the oldest agencies in the federal government. Its origins can be traced back to 1862, when President Abraham Lincoln appointed a chemist, Charles M. Wetherill, to serve in the Department of Agriculture. One of the key early pieces of legislation that initiated the evolution of the FDA into its modern form was the 1906 Pure Food and Drug Act, which prohibited interstate commerce in misbranded drugs, thereby giving the FDA its first regulatory oversight over medical product labeling. The transformation of the FDA took another major step forward in 1938 with passage of the Food, Drug and Cosmetic Act, which gave the FDA authority to require evidence of safety before new drugs could be marketed. Finally, in the 1962 Kefauver-Harris Amendments, the FDA’s drug regulatory authority was expanded to require the FDA to certify drug efficacy and safety before marketing. The Medical Device Amendments in 1976 gave the FDA similar authority to certify the effectiveness and safety of high-risk medical devices before their approval.

Each of these points in the FDA’s early history represented a broadening of its authority and occurred in the context of public health crises related to widely promoted unsafe or ineffective drugs or medical devices, justifying the need for greater government oversight. For example, the Kefauver-Harris Amendments were designed to address the proliferation of medications with poorly documented efficacy and the occurrence of severe side effects caused by some drugs, the most noteworthy example of which was the sedative-antinauseant thalidomide. The 1976 legislation was passed after >100 deaths of young women from a widely promoted, high-risk drug. The passage of the 1962 Kefauver-Harris Amendments foreshadowed the FDA’s broadening of its regulatory authority and occurred in the context of a public health crisis related to a widely promoted unsafe and ineffective healthcare product.

New Drug and Biological Approval Process

There are essentially 3 phases to the development process for most new therapeutic drugs and biologics: preclinical, clinical, and FDA review. The preclinical phase involves assessments of safety and sometimes efficacy of a potential drug candidate in laboratory and animal models. When it becomes clear that the drug is not toxic to animals, the sponsor must submit an Investigational New Drug application to the FDA before human trials can begin. Investigational New Drug applications provide a comprehensive summary of results from animal testing, compound manufacturing, and composition information and describe planned clinical protocols and investigator information for human testing. In allowing an Investigational New Drug to proceed, the FDA makes a determination that human subjects will not be placed at unreasonable risk of harm during clinical testing.

Human clinical testing has traditionally been divided into 3 phases. Phase I trials are focused on drug safety and typically enroll up to a few dozen healthy volunteers. The primary objectives of these dose-ranging studies are to demonstrate safety in humans and to assess the pharmacokinetic and pharmacodynamic properties of the drug such as half-life, metabolism, and excretion. Phase II trials typically enroll up to a few dozen to 100 patients, generating the first safety data in patients who have the disease or condition for which the drug is indicated, and may provide preliminary insight into the efficacy of the drug that can be used to plan subsequent trials. Phase III trials provide the first comparative testing of drug efficacy and safety and may enroll hundreds to thousands of patients with the disease or condition of interest. Higher-quality phase III trials are blinded and randomized, use a comparator, and test clinical end points (eg, mortality, hospitalization, relief of symptoms), as opposed to surrogate markers of disease activity (eg, systolic blood pressure, glycosylated hemoglobin level, tumor progression).

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At the completion of clinical trial testing, the manufacturer submits a formal application for approval, seeking FDA approval for marketing in the United States. This application includes all human and animal studies and information on clinical pharmacology, toxicology, microbiology, chemistry, and manufacturing. The FDA reviews the dossier to assess whether there is substantial evidence of efficacy based on "adequate and well-controlled investigations," as well as adequate evidence of safety, and makes a determination as to whether the benefits of the drug outweigh the risks. The FDA also reviews the manufacturer's planned product labeling and decides to approve the New Drug Application or to request additional information from the manufacturer. The FDA also normally inspects the facilities where the drug will be manufactured.

What defines adequate and well-controlled investigations remains controversial. FDA guidance suggests that 2 phase III trials are preferred, each providing independent evidence of efficacy—such studies are known as pivotal efficacy trials—but also provides flexibility, describing circumstances in which a single efficacy trial might be sufficient to support approval. Legislation in 2007 formally mandated that the FDA allow drug approval on the basis of a single adequate and well-controlled trial in appropriate cases. Research examining pivotal efficacy trials of new drug and biologics approved from 2005 through 2012 found wide variations in the quality of clinical trial evidence that served as the basis of FDA approval. More than one third of indications were approved on the basis of a single pivotal efficacy trial. In addition, only 40% were supported by at least 1 trial that used an active agent as a comparator (as opposed to placebo or no comparator), and 45% were approved on the basis of trials that were focused exclusively on surrogate markers of disease activity. Similarly, fewer than half of new drugs expected to be used for lifelong, continuous treatment were supported by at least 1 trial of ≥6 months. Among the 23 new drugs approved during this period for treatment of cardiovascular disease, the use of surrogate markers of disease activity was higher than for all non-cardiovascular disease drug approvals. These approval decisions influence clinical care. For example, several drugs that effectively lower low-density lipoprotein cholesterol, including ezetimibe, feno- fibrate, and niacin, are now used among large numbers of the population, at great expense, on the basis of only evidence from trials focused on surrogate markers and without clinical trial evidence of their effectiveness for lowering the risk of clinical end points such as death or myocardial infarction.

When a drug is approved via a New Drug Application, it receives 5-7 years of guaranteed market exclusivity, during which time no generic versions of the product can be introduced in the market. This is commonly called the regulatory exclusivity period, and it is extended to a minimum of 7.5 years for nearly all new drugs when potential generic drug entrants bring legal challenges to enter the market (see the generic drug section below). In practice, drug patents maintain effective market exclusivity for new small-molecule drugs for ≥12 to 14 years before competition by generic drugs. As discussed in more detail later, most biological drugs (which are approved by Biologics License Applications) enjoyed indefinite protection from generic competition until recently because there were no clear pathways for approval of follow-on biological drugs.

Important Features and Variations of the New Drug Approval Processes

Prescription Drug User Fees

The Prescription Drug User Fee Act (PDUFA) passed in 1992 authorized the FDA to collect fees from manufacturers submitting new drugs for approval to supplement direct appropriations from Congress. These user fees were enacted at a time when there was widespread dissatisfaction among consumers, industry, and the FDA that the drug approval process was taking too long and that Congressional appropriations to the FDA were too small, although there is evidence that these appropriations had been growing in the years preceding PDUFA. Initially, the user fees were allowed only to support the review of applications and other industry submissions to the agency, but legislation in 2007 allowed some of the funds to also support postmarket safety surveillance activity. User fees now constitute more than $2 billion of the FDA’s $4.5 billion total annual budget. As a quid pro quo, the legislation imposed regulatory performance review deadlines on the FDA such as review of 95% of priority drug applications within 6 months and 95% of standard drug applications within 12 months (shortened to 10 months in 2002). PDUFA requires, and has received, Congressional reauthorization every 5 years since its creation.

After PDUFA was enacted, review times quickly fell from the pre-PDUFA average of 30 months, and there was a spike in new drug approvals after 1992 from the pre-PDUFA backlog that had built up. Annual drug approvals subsequently returned to their historic mean, although there has been an uptick in new approvals in the past 3 years. Currently, the FDA’s approval times are the shortest among regulators worldwide. The average FDA regulatory review time for all new drugs and biologics approved from 2001 through 2010 was ∼10 months, whereas the regulatory review times at the European Medicines Agency and Health Canada were each ∼12 months. However, there is evidence that imposing arbitrary regulatory review deadlines on the FDA may pose a risk to public health. Research has found that the PDUFA requirements concentrated the number of approval decisions made in the weeks immediately preceding the deadline and that, compared with drugs approved at other times, drugs approved in the 2 months before their PDUFA deadlines were significantly more likely than drugs approved at other times to be later found to have important safety risks or to be withdrawn from the market for safety-related reasons. Furthermore, others have raised ethical concerns that the user fee system, whereby nearly half the FDA’s budget is derived directly from manufacturers’ payments, beholds the agency to the industry it regulates.

Orphan Drugs

The Orphan Drug Act was enacted in 1983 by Congress to encourage the development of new drugs for rare diseases likely to otherwise languish in development because they were anticipated to produce low revenues for manufacturers. In 1984, the definition of a rare disease was extended to include conditions that affect <200,000 patients per year in the United States. Manufacturers apply for orphan drug designation from the
FDA during the clinical phase of drug development. If granted, the designation provides a 7-year regulatory exclusivity period starting at the time of approval, recusal from certain FDA fees, and additional tax breaks for the manufacturer’s clinical trials. The orphan drug designation does not formally change the FDA’s standard for approval, but in practice, orphan drugs are more likely than drugs for nonrare diseases to be approved on the basis of phase I and II trials alone or on the basis of trials that use nonrandomized, unblinded designs and test surrogate markers of disease. As would be expected, drugs for rare diseases are also tested in fewer patients overall, with a third as many patients enrolled in pivotal trials for new orphan drugs as for other new drugs. In 2014, the FDA designated a record 291 applications as orphan drugs.

**Expeditied Approval Pathways**

Alternative regulatory pathways facilitate more rapid drug approvals in cases of heightened clinical need. The first of these, initiated by FDA in 1988 (later codified by Congress in 1997), is called the Fast Track program, which is intended for drugs treating serious conditions that fill unmet medical needs, defined by the FDA as one that is not “addressed adequately by an existing therapy.” Manufacturers of fast track drugs are able to meet and communicate more frequently with the FDA to discuss drug development and clinical trial design to ensure collection of appropriate clinical data to support drug approval. The Fast Track program shortens drug development time, likely by allowing approval on the basis of phase I and II trials, and includes requirements for postapproval confirmatory trials. The anticipated benefits of the program remain controversial because comparisons to better understand drug development time and success have been described as challenging.

In 1992, the Accelerated Approval program was initiated for new drugs for serious conditions that fill unmet medical needs, as defined above. Manufacturers of accelerated approval drugs are given special permission by the FDA to focus their clinical trial programs on surrogate markers of disease, rather than clinical end points, and must conduct confirmatory postapproval studies. Although surrogate markers are expected to be good proxies for clinical benefit, a number of concerns have been raised about their reliability and clinical validity, potentially increasing patient and physician uncertainty about the benefits of new drugs approved through this program. Experience with the accelerated approval program has been studied only occasionally. One review of cancer drugs found that confirmatory evidence of safety and efficacy was eventually developed after approval for only 26 of 47 (55%) new drug indications, among which 3 were removed from the market when postapproval studies found no benefit; trials for the remaining 18 had not yet been completed at the time of the review. Few cardiovascular drugs have received accelerated approval. Midodrine, an α1-adrenergic agonist, was granted accelerated approval for treatment of symptomatic orthostatic hypotension in 1996. As of August 2010, none of the postmarketing studies required by the FDA to demonstrate clinical efficacy had been completed, and the FDA proposed withdrawing the medication, a decision later overturned after protests from patients and clinicians. It remains unclear whether trials have since been completed.

The latest effort by Congress to facilitate more rapid drug approvals by the FDA was the Breakthrough Therapy designation, introduced in 2012. Eligible drugs must be used to treat serious conditions and must have preliminary clinical evidence demonstrating potential for real improvement over standard of care. Although the designation does not formally change the FDA’s standard for review, a breakthrough therapy can be approved on the basis of abbreviated or combined traditional clinical phases. For example, the legislation seems to permit designation based on “an effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate end point.” This will naturally limit the evidence available to inform patient and physician decisions about these new drug therapies at the time of their FDA approval. Experience with drugs approved under the Breakthrough Therapy designation is just beginning and includes such widely lauded drugs as sofosbuvir (Sovaldi) for hepatitis C and supplemental indications for the cystic fibrosis drug ivacaftor (Kalydeco). One cardiovascular drug that received this designation was AAIV1/SERCA2a (Mydicar), a genetically targeted enzyme replacement therapy for heart failure patients, although this drug later did not show significant improvement in cardiovascular outcomes in a Phase 2 trial. Over 80 other investigational drugs have been tagged with this designation. During the past 20 years, these alternative expedited approval pathways have become the norm rather than the exception. Approximately half of new drug and biologics approved for use in the past decade used 1 or more of pathways intended to make therapeutically important drugs available at an earlier time, and that fraction appears to be rising.

**Generic Drug Approval Process**

Once the regulatory- and patent-based market exclusivities for a brand-name drug end, generic manufacturers of the product may enter the market. Generic drugs are identical to brand-name drugs in dose form, route of administration, and intended use. Generic drugs may differ in superficial features such as pill color or shape, as well as inactive ingredients. Until 1984, the generic drug market was limited because the FDA required most generic manufacturers to provide full demonstration of safety and efficacy, similar to brand-name drug approvals. Because of the time and expense required to conduct clinical trials, among 150 brand-name drugs approved after 1962 for which patent exclusivity protections had concluded, generic versions were available on the market for only 15. In 1984, Congress passed the Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act, which allowed the FDA to approve generic drugs on the basis of bioequivalence, or the determination of no significant difference in the availability or absorption of the active ingredient at the site of drug action. Generic manufacturers still must satisfy other regulatory requirements, including labeling, pharmacology/toxicology, chemistry, manufacturing, and inspection. Because research and development costs of generic drugs are far lower than for brand-name drugs and because there is competition among bioequivalent generic drug manufacturers,
generic drug prices are much less than the prices of brand-name drugs. Substitution of low-cost generic drugs has saved consumers >$1 trillion in the last decade alone. Moreover, there are clear clinical care benefits to generic drug use because their low cost is associated with improved patient adherence compared with brand-name drugs. A recent study comparing the efficacy of generic and brand-name statins found improved clinical outcomes among generic statin users, likely in part because of improved adherence to the lower-cost therapy.

In addition, despite generic drugs being cheaper, they remain equally effective. One systematic review and meta-analysis identified 38 head-to-head randomized, controlled trials that compared the clinical efficacy of generic and brand-name cardiovascular drugs among 9 subclasses of medications, the vast majority of which were conducted during the 1980s and 1990s. Clinical equivalence was demonstrated for 35 of these comparisons (92%), with only 1 of 11 comparisons of diuretic therapies and 2 of 7 comparisons of calcium channel blockers not finding equivalence. Currently, >8 in 10 prescriptions filled in the United States are for generic drugs, and this rate is likely higher for commonly prescribed cardiovascular medications such as cholesterol-lowering statins. Widespread use of generic drugs occurs in part because of state pharmacy laws that promote generic drug use by allowing substitution of FDA-approved generic drugs when a physician writes a prescription for a brand-name drug. Nearly all states also allow patients or the prescribing physician to request the brand-name formulation, although their health insurers may charge more for this choice.

Barriers to Generic Competition

Brand-name manufacturers use many strategies to delay generic competition as long as possible, a practice called lifecycle management, and it would be impossible to review all of those strategies here. One of the most common of such strategies relies on the fact that all pharmaceutical manufacturers frequently patent peripheral aspects of their approved drug products, including metabolites, alternative crystalline structures, or the coating of the pill, and use these later-issued patents to block generic approval even after the patent on the original active ingredient has expired. The Hatch-Waxman Act included an incentive to encourage generic manufacturers to design around and challenge brand-name drug manufacturers’ patents in court, reducing the chance that these secondary patents would excessively extend brand-name market exclusivity. That legislation provided a 180-day period of generic market exclusivity for the first manufacturer mounting a successful challenge that leads to generic drug approval, essentially creating a duopoly that would artificially inflate generic prices for that period.

In the past decade, many of these Hatch-Waxman patent challenge cases have ended in settlements between the brand-name and generic manufacturers. Some of those settlements have come under scrutiny by the Federal Trade Commission because they involved massive payments from the brand-name company to the generic company in exchange for dropping its patent challenge and consequently delaying marketing of its generic drug until a date closer to the end of the patent term. These payments look like anticompetitive business deals between the 2 companies and have been referred to as pay-for-delay deals. Annual reports by the Federal Trade Commission indicate that generic versions of as many as 142 brand-name drugs have been delayed by pay-for-delay arrangements between drug manufacturers since 2005 and that these arrangements are expected to lead to $35 billion in excess drug spending over the 2010 to 2020 period. A focused review of the top 20 of these drugs, including well-known cardiovascular therapies such as aspirin and extended-release dipyridamole (Aggrenox), amlodipine/atorvastatin (Caduet), atorvastatin (Liptor), and extended-release niacin (Niaspan), found that these agreements delayed generic drugs for 5 years on average and for as long as 9 years, during which time the brand-name drug companies made an estimated $98 billion in sales. In 2013, the Supreme Court ruled that settlements involving payments can be challenged by the Federal Trade Commission, although whether a particular settlement is actually anticompetitive will be determined by the circumstances of the case.

Biosimilar Approval

The foregoing discussion of the generic drug approval process has applied only to so-called “small-molecule” drugs, in part because the Hatch-Waxman Act did not apply to most biological drugs. Biological drugs are large-protein therapeutics such as monoclonal antibodies or enzymes usually made from living cells. There was no pathway for approval of follow-on versions of biological drugs in the United States until 2009, when Congress passed the Biologics Price Competition and Innovation Act, one of many components of the Patient Protection and Affordable Care Act. In Europe and other places where follow-on biologics (also called biosimilars) for products have been available since the mid-2000s, these products have led to anywhere between 2% and 73% reductions in prices. One of the primary concerns has been that biologics are much more complex than small-molecule drugs, and it is still an unanswered question whether biologics produced by different manufacturers, but not subject to the same clinical testing, can be confirmed to have similar efficacy or can be substituted in routine patient care without causing immunological or unexpected side effects. The act gives the FDA the option of approving follow-on biologics as interchangeable or noninterchangeable, and the preclinical testing required of follow-on biologics will be more extensive than that for small-molecule generics and will be based on the type of biological drug.

In March 2015, the first follow-on biologic was approved by the FDA, filgrastim-sndz (Zarxio), a version of the granulocyte colony stimulating factor filgrastim (Neupogen), although its launch was delayed until September due to litigation.

Generic Drug User Fees

Under the Generic Drug User Fee Amendments (GDUFA), introduced in 2012, generic drug manufacturers have for the first time been required to pay user fees, akin to PDUFA. The purpose of these fees is to facilitate the review of the large backlog of generic drug applications that had developed and
to provide additional funding to the FDA for inspections of
generic drug manufacturing facilities, particularly overseas.
Initially, several factors complicated GDUFA implementa-
tion, including slower-than-expected registration by generic
manufacturers and difficulty knowing which overseas facili-
ties need to register. Under GDUFA, the FDA’s review time
commitments are much shorter than the average pre-GDUFA
review times for generic drug applications, so there is wide-
spread expectation that generic drug applications will be
approved more expeditiously.

Medical Device Approval Process
The Medical Device Amendments of 1976 established 2
major pathways through which the FDA could review novel
medical devices: premarket approval (PMA) and 510(k) clear-
ance pathways. The pathway through which a device is autho-
rized for marketing depends on the risk associated with its use,
the patient population that stands to benefit from the device,
and the existence of similar devices on the market. Class I
devices are the lowest risk and include products such as ban-
dages, tongue depressors, and walking canes. Class II devices
pose moderate/intermediate risk to patients but have estab-
lished performance standards and include products such as
contact lens solutions and hearing aids. Although neither class
I nor class II medical devices are intended to be used in sup-
sorting or sustaining human life, several devices that might be
interpreted as meeting this criterion, including hip and knee
implants, have been classified as class II. Class III devices are
the highest risk and include products such as implantable car-
diac pacemakers, stents, and heart valves.

The PMA pathway is intended to evaluate high-risk
devices for which there are no commercially distributed prec-
edents. Applications require clinical testing that provides rea-
sonable assurance that the device is safe and effective for its
intended use. The FDA reviews the planned product labeling
and conducts manufacturing inspections before clearing the
PMA or requesting additional information from the manufac-
ufacturer. Notably, the strength of the evidence underlying PMAs
can vary. In a study examining 78 high-risk cardiovascular
devices that received market clearance by the FDA through the
PMA pathway from 2000 through 2007, 65% were found to
have been approved on the basis of a single trial. Moreover,
only 27% of these trials were randomized, 14% were blinded,
and half had a comparison group (one third of which were his-
torial controls), and nearly 90% of end points were focused
on surrogate markers of disease.

The 510(k) pathway generally provides clearance of mod-
erate-risk devices. The 510(k) clearance does not require clin-
cial trials that demonstrate safety and effectiveness. Instead,
the manufacturer must demonstrate that the device is sub-
stantially equivalent in materials, purpose, and mechanism of
action to another device already on the market, referred to as
the predicate device. In fact, the pathway allows the use of
multiple predicates, and reports have found devices cleared
on the basis of predicates that have been voluntarily recalled.
The 510(k) pathway can allow manufacturers to make small
improvements on already marketed devices and allow compa-
nies with new products to compete with very similar devices
without undergoing extensive clinical testing. The pathway
has been criticized, including by the Institute of Medicine,
which described the pathway as “unable to optimally protect
patients.” From 2003 through 2007, 67% of class III medi-
cal devices received market clearance via the 510(k) path-
way as opposed to the PMA pathway. In the last few years,
the FDA has gone through a rigorous process of re-evaluating
some 510(k)-cleared devices to ensure that devices are appro-
priately classified on the basis of potential risk. For example,
advanced external defibrillators are class III devices, many
of which received 510(k) clearance. However, in response
to thousands of reports of device failure or malfunction, as
well as numerous recalls, the FDA issued a proposed order
in March 2013 to require PMA pathway clearance for these
devices.

Additional Features of the Medical
Device Approval Process
Humanitarian Device Exemption Pathway
In 1990, Congress passed the Safe Medical Devices Act, which
led to the creation of the Humanitarian Device Exemption
(HDE) pathway. The HDE pathway is available only to
humanitarian use devices, defined as any device intended to
benefit patients by treating or diagnosing a disease or condi-
tion that affects <4000 individuals in the United States annu-
ally. The HDE pathway requirements are similar to those of a
PMA, but HDE applications are exempt from the effectiveness
requirements and must submit only sufficient clinical testing
for the FDA to determine that the device does not pose an unrea-
sonable or significant risk of illness or injury and that the
probable benefit outweighs any risk. Because manufacturers’
research and development costs could exceed market returns
for diseases or conditions affecting small patient popula-
tions, the HDE pathway can help motivate the development of
devices for these rare diseases, for which patients may have no
other treatment alternatives. Some commentators have raised
concerns that manufacturers may choose to pursue HDE path-
way approval for narrow indications, even for devices likely to
be used in broader patient populations. For example, 2 patent
foramen ovale occluders received HDE pathway clearance in
2006 for the treatment of patients with recurrent cryptogenic
stroke resulting from presumed paradoxical embolism through
a patent foramen ovale and who have failed conventional drug
therapy; however, the FDA withdrew their HDE clearance in
2012 when it became clear that the target population for use
of the devices exceeded the statutory threshold. Others have
raised concerns that follow-up formal confirmatory testing of
HDE devices should be performed because a review of pedi-
atric HDE clearances suggested such testing may not be hap-
pening consistently.

PMA Supplement Pathway
High-risk medical devices originally cleared by the FDA
through the PMA pathway can be iteratively changed and
redesigned and receive more rapid approval in their modified
form, without additional clinical effectiveness or safety evi-
dence, through the PMA supplement pathway. Such supple-
ments may include major or minor design changes and routine
changes in labeling, materials, or packaging. From 1979 to
2012, the FDA cleared 77 initial PMA and 5829 supplement PMA applications for cardiac implantable electronic devices, with a median of 50 supplements (interquartile range, 23–87) per initial PMA pathway clearance.75 Nearly all cardiac implantable electronic device models currently used by clinicians received marketing clearance via PMA supplements.75 At what point multiple device modifications may change the underlying safety or effectiveness profile and require clinical testing is unknown but deserves further consideration.76

Medical Device User Fees
Similar to PDUFA and GDUFA, the Medical Device User Fee Act was enacted in 2002 and authorizes the FDA to collect fees from medical device companies to supplement direct appropriations from Congress to support the review of PMAs, 510(k) clearances, and other industry submissions to the agency. The act established performance goals for the agency such as issuing marketing decisions for PMA submissions within either 180 or 320 days, depending on the need for advisory committee input, or for 510(k) submissions within 90 days. The Medical Device User Fee Act requires Congressional reauthorization every 5 years, which most recently occurred in 2012. A recent examination of the FDA’s medical device review process, including adherence to Medical Device User Fee Act performance goals, found that class III medical devices approvals required nearly 400 days of FDA review from 2002 through 2007, have lengthened in duration since 2005, and rarely met Medical Device User Fee Act statutory deadlines.77 However, other reports have found that the time required to bring a new device to market in the United States through the FDA is similar to, if not shorter than, the time required in the United Kingdom, France, Italy, and Germany, once regulatory and national payer evaluations are taken into consideration.78

Postmarket Surveillance of Drugs, Biologics, and Medical Devices
A great deal is learned about drug and medical device safety once they are being used actively among patients as prescribed by physicians. A key responsibility of the FDA is to monitor the ongoing safety and effectiveness of medical products, and to do this, the FDA has traditionally relied most heavily on postmarket surveillance programs that passively aggregate adverse events: the FDA Adverse Event Reporting System for drugs and the Manufacturer and User Facility Device Experience Database for medical devices. Both are databases that contain information on adverse event reports submitted to the FDA, the vast majority of which are submitted on a voluntary basis by healthcare professionals, patients, and industry representatives. Although the FDA Adverse Event Reporting System and the Manufacturer and User Facility Device Experience Database have successfully detected potential safety issues and contributed to benefit-risk reassessments, passive surveillance systems have clear limitations, including the submission of incomplete, inaccurate, untimely, unverified, or biased data.79,80 In addition, the incidence or prevalence of an event cannot be determined from these reporting systems alone because of underreporting of events and lack of information about frequency of drug or device use.79,80

To supplement the safety information ascertained through these systems, the FDA can also require that manufacturers conduct postmarket studies at the time of market approval, also referred to as phase IV studies. For medical devices, postapproval studies, including clinical trials and product registries, are often required at the time the device is cleared through the PMA and HDE pathways. In addition, postmarket surveillance studies, sometimes referred to as 522 studies, can be required when safety concerns are identified after a medical device is available for use; these studies are generally used for devices that received 510(k) clearance. Approximately half of drug and biological approvals between 1990 and 2004 included at least 1 postmarket study commitment, three quarters of which were clinical studies.81,82 Similarly, approximately half of PMA and HDE devices approved since 1995 have been subject to at least 1 FDA-mandated postapproval study. However, problems have been described in the conduct of postmarket study commitments, including an inability to track completion of studies and to communicate ascertained information to the public and healthcare professionals. As described further below, the FDA has limited authority to enforce these commitments or to penalize manufacturers that do not undertake them in a timely manner.82

Postmarket safety surveillance is particularly salient to the field of cardiology because thromboembolic events and cardiac arrhythmias are among the most severe drug- or device-related adverse events experienced by patients. In addition, because many of the clinical trials leading to product approval are of short duration and study relatively small numbers of patients, there may not be sufficient observed patient-time of exposure for adverse event risk to be detected in the trials reviewed by the FDA. For example, the cardiovascular risk associated with rofecoxib (Vioxx) became most obvious several years after drug approval and eventually led to its market withdrawal.83 Nearly a decade had passed after the approval of rosiglitazone (Avandia) before the risk of acute myocardial infarction was identified.84 More recently, dronedarone (Multaq), a drug used to restore sinus rhythm and to reduce hospitalization or death in intermittent atrial fibrillation,85 was found to increase the risk of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation.86 In both the rosiglitazone and dronedarone cases, the safety concerns identified led the FDA to require that the manufacturers initiate Risk Evaluation and Mitigation Strategies, which included developing medication guides for patients, communication plans for physicians, and elements for safe use, which are certifications or other controls to direct drug therapy to patients for whom the benefits outweigh the risks.87 Postmarket safety surveillance is perhaps even more critical for cardiovascular devices because devices can be cleared for marketing without new clinical data through the 510(k) pathway or with limited data of short duration through the PMA pathway, even for implantable devices. Moreover, few postmarket clinical trials are conducted for high-risk medical devices approved via the PMA pathway, such that limited information is generated to inform device safety after approval.65a For instance, both the Sprint Fidelis and the Riata and Riata ST implantable cardioverter-defibrillator leads were
recalled after the manufacturers identified increased risks of lead fracture and failure, respectively.88,89

**Recent Changes to Postmarket Surveillance of Drugs, Biologics, and Medical Devices**

**FDA Amendments Act**
A series of highly publicized drug withdrawals in the 2000s, including rofecoxib,90 prompted a re-examination of the FDA's postmarket surveillance system. The Institute of Medicine recommended that the FDA more closely monitor and evaluate the benefits and risks of drug therapies not only before their approval but throughout their entire market life.91 This approach involves the pursuit and active management of emerging knowledge about the benefit-risk balance as products become more widely used by larger numbers of increasingly diverse patients.92 In 2007, Congress passed the FDA Amendments Act and provided the agency with additional resources to evaluate drug-safety issues and new authorities to require postmarket studies. Since 2007, there has been an increasing number of mandated postmarketing studies: 46 in 2008 and 387 as of 2011.93 Still, postmarket studies remain plagued by delays.93

**Sentinel Initiative**
The FDA Amendments Act also required that the FDA work with public, academic, and private entities to develop a data system to obtain information from existing electronic healthcare data (primarily administrative claims data gathered by insurers and other payers) to proactively assess medical product safety. Through this legislation, the Sentinel Initiative was established and launched as the Mini-Sentinel program in 2008. The program uses a distributed data approach in which data partners retain control over electronic healthcare data routinely collected via their healthcare delivery system as a result of normal activities but execute standardized computer programs to conduct specific analyses and share aggregated results.94,95 Mini-Sentinel engages in active surveillance by conducting pre-specified queries using the distributed data network and does not require patients or clinicians to initiate reports to FDA. The program has made substantial strides toward developing data partners, establishing functional processes and methods, and leveraging big data for regulatory science and public health safety.96 Outstanding issues include how to reconcile differing results from clinical trials and the Mini-Sentinel program. For example, a recent analysis found that the Mini-Sentinel program query for gastrointestinal tract bleeding risk associated with dabigatran compared with warfarin found exactly the opposite of results from a meta-analysis of randomized, clinical trials.97

**Unique Device Identifiers**
The Mini-Sentinel program is currently best suited for active postmarket surveillance of drugs rather than medical devices because medical devices cannot be identified with administrative claims. Another key provision of the FDA Amendments Act required the FDA to establish a Unique Device Identification System. Since September 2014, labels and packages of class III medical devices have included Unique Device Identifications, numbers assigned by the manufacturer to a version or model of a device that confer production-specific information, including the lot number of the product and manufacturing and expiration dates. All medical devices should have a Unique Device Identification as of 2020. The FDA also plans to create a publicly searchable database called the Global Unique Device Identification Database that will serve as a reference catalog to understand device background and history.98

**Summary**
Our review of the approval and postmarket surveillance of new drug and biological therapies, generic drugs, and medical devices shows the range of the FDA’s authorities and responsibilities and highlights areas of effective regulatory oversight, as well as some important limitations to the FDA’s authority with direct implications for patient care. We have demonstrated that the FDA has numerous pathways that allow rapid authorization of promising new drugs and devices to address unmet medical needs and generally performs its functions as quickly as, if not more quickly than, its counterparts in other countries. However, the choice of approval pathway for both drugs and devices clearly affects the evidence generated to support FDA approval, information that should be clearly communicated to patients and physicians. In addition, postmarket surveillance remains a challenge with methodological and resource limitations. As the healthcare marketplace is confronted with new and innovative medical products such as mobile health devices, 3-dimensional printers, follow-on biologics, targeted gene therapies, and even medical marijuana, it will be important to learn from the FDA’s past experiences in designing policies that optimize its ability to protect the public health.

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