

# FDA Approval and Regulation of Pharmaceuticals, 1983-2018

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**IMPORTANCE** US law requires testing of new drugs before approval to ensure that they provide a well-defined benefit that is commensurate with their risks. A major challenge for the US Food and Drug Administration (FDA) is to achieve an appropriate balance between rigorous testing and the need for timely approval of drugs that have benefits that outweigh their risks.

**OBJECTIVE** To describe the evolution of laws and standards affecting drug testing, the use of new approval programs and standards, expansions of the role and authority of the FDA, and changes in the number of drugs approved from the 1980s to 2018.

**EVIDENCE** Sources of evidence included principal federal laws and FDA regulations (1962-2018) and FDA databases of approved new drugs (1984-2018), generic drugs (1970-2018), biologics (1984-2018), and vaccines (1998-2018); special development and approval programs (Orphan drug [1984-2018], Fast-Track [1988-2018], Priority Review and its predecessors [1984-2018], Accelerated Approval [1992-2018], and Breakthrough Therapy [2012-2018]); expanded access (2010-2017) and Risk Evaluation and Mitigation Strategies (2008-2018); and user fees paid to the FDA by industry (1993-2018).

**FINDINGS** From 1983 to 2018, legislation and regulatory initiatives have substantially changed drug approval at the FDA. The mean annual number of new drug approvals, including biologics, was 34 from 1990-1999, 25 from 2000-2009, and 41 from 2010-2018. New biologic product approvals increased from a median of 2.5 from 1990-1999, to 5 from 2000-2013, to 12 from 2014-2018. The median annual number of generic drugs approved was 136 from 1970 to the enactment of the Hatch-Waxman Act in 1984; 284 from 1985 to the enactment of the Generic Drug User Fee Act in 2012; and 588 from 2013-2018. Prescription drug user fee funding expanded from new drugs and biologics in 1992 to generic and biosimilar drugs in 2012. The amount of Prescription Drug User Fee Act fees collected from industry increased from an annual mean of \$66 million in 1993-1997 to \$820 million in 2013-2017, and in 2018, user fees accounted for approximately 80% of the salaries of review personnel responsible for the approval of new drugs. The proportion of drugs approved with an Orphan Drug Act designation increased from 18% (55/304) in 1984-1995, to 22% (82/379) in 1996-2007, to 41% (154/380) in 2008-2018. Use of Accelerated Approval, Fast-Track, and Priority Review for new drugs has increased over time, with 81% (48/59) of new drugs benefiting from at least 1 such expedited program in 2018. The proportion of new approvals supported by at least 2 pivotal trials decreased from 80.6% in 1995-1997 to 52.8% in 2015-2017, based on 124 and 106 approvals, respectively, while the median number of patients studied did not change significantly (774 vs 816). FDA drug review times declined from more than 3 years in 1983 to less than 1 year in 2017, but total time from the authorization of clinical testing to approval has remained at approximately 8 years over that period.

**CONCLUSIONS AND RELEVANCE** Over the last 4 decades, the approval and regulation processes for pharmaceutical agents have evolved and increased in complexity as special programs have been added and as the use of surrogate measures has been encouraged. The FDA funding needed to implement and manage these programs has been addressed by expanding industry-paid user fees. The FDA has increasingly accepted less data and more surrogate measures, and has shortened its review times.

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The US Food and Drug Administration (FDA) plays a central role in patient care and the economy. The FDA implements standards established by Congress regarding prescription drug effectiveness and safety so that clinicians and patients can reliably expect that approved drugs will have a beneficial effect and be reasonably safe. Confidence in the value of new medicines and the unusual nature of prescription drug reimbursement in the United States have helped create one of the largest industries in the world: spending in the United States on retail and in-hospital prescription drugs (including amounts retained by pharmacies, hospitals, physician practices, and other intermediaries) was more than \$400 billion in 2016.<sup>1,2</sup>

Regulatory authority was originally based on the 1906 Pure Food and Drug Act, enacted to address the widespread use of over-the-counter medications that often included dangerous and undisclosed ingredients like opium, alcohol, or cocaine. But this act required only that medications accurately list their ingredients, not that they be dispensed only after a physician's prescription or be shown to be safe and effective. After 3 decades in which many potentially unsafe drugs were sold without any preapproval clinical testing, the 1938 Food, Drug, and Cosmetic Act required that a drug be shown to be nontoxic, but the act had no explicit efficacy requirement and allowed marketing if the FDA had not taken action within 60 days. In 1962, in the wake of the thalidomide crisis in which an anti-nausea/sedative drug widely used outside the United States was found to cause severe birth defects, Congress formally required evidence of efficacy before a drug could be approved. During the past half-century, the nation has often reassessed the FDA's approach to drug evaluation, and its role has evolved through internal rule changes and new legislation, beginning with the Orphan Drug Act of 1983 through the 21st Century Cures Act of 2016 (Figure 1).

This Special Communication describes the evolution of laws and standards that have affected drug testing, the use of new approval programs and standards, expansions of the role and authority of the FDA, and changes in the number of drugs approved from the 1980s to 2018.

## Methods

Sources of evidence included principal federal laws and FDA regulations (1962-2018) and FDA databases of approved new drugs (1984-2018), generic drugs (1970-2018), biologics (1984-2018), and vaccines (1998-2018); special development and approval programs (Orphan drug [1984-2018], Fast-Track [1988-2018], Priority Review and its predecessors [1984-2018], Accelerated Approval [1992-2018], and Breakthrough Therapy [2012-2018]); expanded access (2010-2017) and Risk Evaluation and Mitigation Strategies (2008-2018); and user fees paid to the FDA by industry (1993-2018).

This review includes information on new molecular entities approved by the FDA's Center for Drug Evaluation and Research (CDER) following a New Drug Application (NDA), as well as biologics licensed by CDER under a Biologics License Application (BLA) (see Box 1 for definitions of terms used in this article).

Drugs benefiting from expedited development or review programs were identified by examining the FDA's annual new drug approval reports (2011-2018) and the Drugs@FDA database (1984-2010); identified programs were then cross-checked with FDA lists that summarize use of expedited programs (1983-2018) and infor-

## Key Points

**Question** How has the regulation of prescription drugs evolved from the 1980s to 2018, and what trends have occurred in drug approvals?

**Findings** Approvals of new generic drugs have increased over time, leading to greater competition. Technological advances have been reflected in increased approvals of biologics over time. The number of expedited development and approval programs has expanded greatly since 1983, reducing the amount of evidence available at the time of approval and increasing uncertainty about the existence or amount of clinical benefit. These regulatory innovations have not clearly led to an increase in new drug approvals or to reduced total development times.

**Meaning** While retaining policies that encourage efficient review, Congress and other government officials should also consider the implications of less rigorous clinical outcome requirements and whether the current complex array of regulatory programs should be simplified.

mation obtained from the FDA under the Freedom of Information Act. When making temporal comparisons of program usage or other data, the data were divided into 2 or 3 periods of approximately equivalent duration, depending on the dates for which data were available.

Development times and review durations for all new drugs approved between 1987 and 2017 were calculated as the time from the effective date of the Investigational New Drug application (IND), which authorizes the commencement of clinical trials, to approval of the associated NDA or BLA.

The FDA often requests or requires that manufacturers perform additional studies of a drug after it has been approved for use, although its ability to compel such studies is weaker than in the preapproval phase. To determine whether such postmarket requirements and postmarket commitments were completed or were no longer required, data from the Federal Register and academic literature were analyzed.<sup>3</sup> Additional postmarketing utilization requirements (Risk Evaluation and Mitigation Strategies) are sometimes established by the agency to improve the appropriateness of use of drugs with important preventable adverse effects. Data on these requirements were obtained from the FDA.<sup>4</sup>

## Results

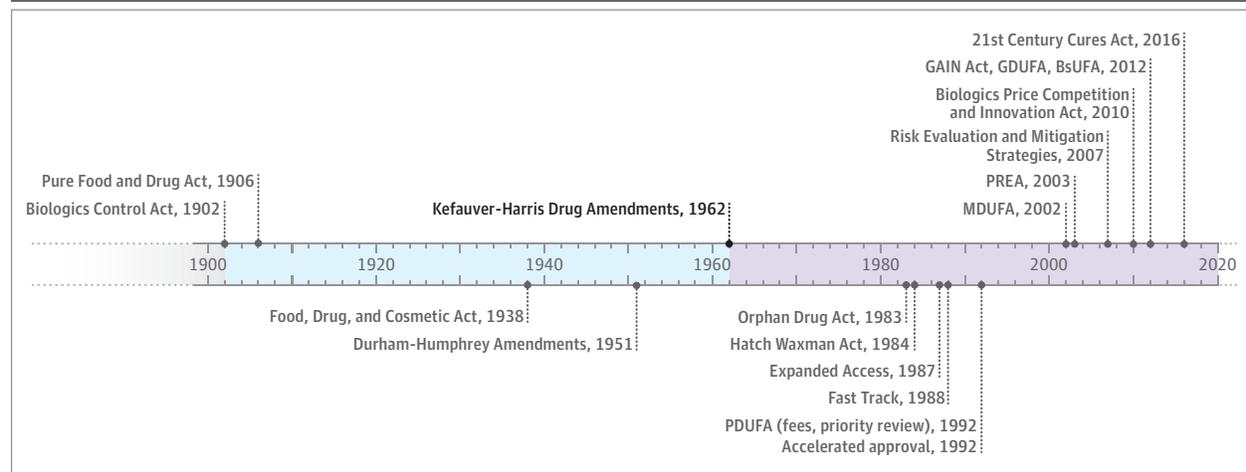
### FDA Operations

In 2017, the FDA spent \$1.55 billion to regulate human drugs and biologics and collected \$1.22 billion (79%) of this from pharmaceutical manufacturers in required user fees (see below), including \$837 million in branded drug user fees, \$356 million in generic drug user fees, and \$29 million in biosimilar user fees.<sup>5,6</sup>

### User Fees: The Law

After the 1962 Kefauver-Harris Drug Amendments prohibited marketing without explicit FDA approval based on documentation of efficacy, budget limitations made it impossible for the FDA to hire sufficient personnel to timely process the increasingly large volumes of data that accompanied new drug applications, and FDA review times increased to more than 30 months by the early 1980s.<sup>7</sup> In the

Figure 1. Timeline of Landmark Legislation and Regulations Relating to FDA Authority to Regulate Drugs



After the 1962 Kefauver-Harris Drug Amendments (left), a series of legislative enactments and regulatory programs (right) progressively increased the flexibility of evidence requirements and imposed expanding user fees to fund the drug approval process. BsUFA indicates Biosimilar User Fee Act; FDA,

US Food and Drug Administration; GAIN, Generating Antibiotic Incentives Now; GDUFA, Generic Drug User Fee Act; MDUFA, Medical Device User Fee Act; PDUFA, Prescription Drug User Fee Act; PREA, Pediatric Research Equity Act. Sources: Hein Online (statutes); Federal Register (FDA regulations).

late 1980s, this led to demonstrations at FDA headquarters by AIDS activists concerned that the agency was failing to expeditiously approve lifesaving treatments.

To generate the funds needed to accelerate review times, Congress in 1992 enacted the Prescription Drug User Fee Act, which authorized the collection of fees to be paid by the pharmaceutical industry when submitting a new drug application.<sup>8</sup> This was coupled with negotiated targets for review timeliness: most standard NDAs would be reviewed within 12 months (shortened to 10 months by 2002<sup>9</sup>), while most priority NDAs (for drugs seen as representing a therapeutic advance, as determined by the FDA) would be reviewed in 6 months. Total drug user fees collected (excluding generic and biosimilar drug fees) increased from \$0.3 billion between 1993 and 1997 (Prescription Drug User Fee Act [PDUFA] 1) to \$4.1 billion between 2013 and 2017 (PDUFA 5). Annual fees collected under PDUFA have increased from \$29 million in 1993 to \$908 million in 2018 (Figure 2).

Review times declined sharply, and the legislation proved popular with industry, although questions have been raised about the effect of such a high proportion of FDA staff salaries being provided by industry.<sup>10</sup> Since 1992, the program has been reauthorized and expanded every 5 years, often in legislation containing additional provisions affecting the FDA.

### User Fees and Approval Times

Reducing review times has been seen as a means of getting drugs to patients more quickly as well as allowing pharmaceutical companies to realize sales revenues sooner. Median FDA review times for both standard and priority applications, including all cycles of review, declined from 2.8 years in 1986-1992, to 1.5 years in 1993-2005, to 1.2 years in 2006-2017. By 2018, median review time was 10.1 months for standard applications (n = 79) and 7.6 months for priority applications (n = 43) (Figure 3). At each 5-year renewal of PDUFA, fees were increased and new user fees programs were added for medical devices (2002), generic drugs (2012), and biosimilars (2012).

Priority Review has been used for an increasing proportion of new applications since 1992. If the FDA declined to approve a drug during its first review cycle, it was required to issue a "complete response letter" identifying the deficiencies that a sponsor must address.<sup>11</sup> By the 2015-2018 period the FDA approved 90% of 172 drugs (both priority and standard) after just 1 review cycle, compared with 77% of 137 drugs from 2011 to 2014. Since 1988, the FDA has approved approximately 80% or more of submitted NDAs and BLAs.<sup>12</sup> FDA internal review times have shortened and are now equal to or shorter than review times of other regulators around the world.<sup>13</sup> However, the total time from the IND effective date to final approval, which also includes a manufacturer's development activities, averaged 7.8 years from 1986-1996, 7.0 years from 1997-2007, and 9.1 years from 2008-2017 (Figure 3).

### Preapproval

#### Preapproval Testing: The Law

The 1962 Kefauver-Harris Amendments required a sponsor (generally the drug's manufacturer) to submit an IND before beginning human trials that summarized the available information about the drug's effects in the laboratory and in animals. The IND was also required to set forth a protocol for human studies, which were later divided into 3 phases.<sup>14,15</sup>

Phase 1 studies are uncontrolled studies in humans, generally involving 20 to 80 healthy volunteers, and are intended to gather information about pharmacokinetics and pharmacodynamics, to initially assess a drug's safety at varying doses, and in some cases (such as chemotherapy) to obtain preliminary evidence of efficacy.<sup>16</sup> Phase 2 trials evaluate adverse effects and efficacy in up to a few hundred participants with the condition under study.<sup>16</sup> Despite their formal definition,<sup>16</sup> phase 2 trials generally have no comparison group, are often not blinded or randomized like phase 3 trials, and often use laboratory tests or imaging studies (surrogate measures) to assess results. Phase 3 trials usually include several hundred to several thousand patients. Ideally, these studies use concurrent

**Box 1. Definitions**

**21st Century Cures Act (2016).** US legislation authorizing funds for the Precision Medicine Initiative and Cancer Moonshot; encouraging the use of patient-reported outcomes, surrogate measures, and real world evidence in drug approval; and creating a limited population pathway for antibiotics, among other initiatives.

**Abbreviated New Drug Application (ANDA).** Application submitted to the FDA seeking approval of a generic version of a previously approved drug.

**Biologics License Application (BLA).** Application submitted to the FDA seeking approval of a new biologic product.

**Biologics Price Competition and Innovation Act (BPCIA) (2010).** Enacted as part of the US Patient Protection and Affordable Care Act, the BPCIA created an abbreviated pathway for follow-on biologic products analogous to the Hatch-Waxman Abbreviated New Drug Application pathway for small-molecule drugs.

**Breakthrough Therapy designation (2012).** A designation created by the 2012 FDA Safety and Innovation Act and applicable to experimental drugs that, based on preliminary clinical evidence, may demonstrate substantial improvement over existing therapies on 1 or more clinically significant end points.

**Center for Biologics Evaluation and Research (CBER).** A part of the FDA responsible for regulating blood products, tissues, vaccines, and cellular and gene therapies.

**Center for Drug Evaluation and Research (CDER).** A part of the FDA responsible for regulating over-the-counter and prescription drugs, including most therapeutic biologics.

**FDA Amendments Act (2007).** US legislation renewing user fees for drugs and devices, creating the Risk Evaluation and Mitigation Strategies program, and authorizing the Sentinel Initiative, among other provisions.

**Generating Antibiotic Incentives Now (GAIN) Act.** As part of the 2012 FDA Safety and Innovation Act, GAIN authorized an extension by 5 years of existing 3-, 5-, and 7-year nonpatent exclusivities, for certain antibacterial and antifungal products.

**Hatch-Waxman Act (1984).** Landmark legislation responsible for catalyzing the modern generic drug industry by authorizing an Abbreviated New Drug Application pathway for drugs approved after 1962 and creating a special challenge process for brand-name drug patents.

**Investigational New Drug Application (IND).** A submission required to be made to the FDA before initiating human drug trials.

**New Drug Application (NDA).** A submission required to be made to the FDA after completion of human drug trials and before marketing.

**New Molecular Entity (NME).** An active ingredient that contains no active moiety that has been previously approved by the FDA or has been previously marketed as a drug in the United States.

**Orange Book.** A publication of the FDA that lists approved prescription drug products and patent and nonpatent exclusivities; formally entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" and available in electronic format.

**Patent term restoration.** A provision of the 1984 Hatch-Waxman Act allowing extensions of up to 5 years (but in no case extending more than 14 years after approval) for 1 patent for each product subject to a regulatory review period, to compensate for patent time lost because of the conduct of clinical trials and regulatory review.

*(continued)***Box 1. (continued)**

**Pediatric Research Equity Act (2003).** US legislation requiring results from pediatric assessments to be submitted as part of new drug applications unless granted a waiver by the FDA.

**Phase 1.** Uncontrolled human studies generally involving 20 to 80 healthy volunteers that are primarily intended to gather information about a drug's pharmacokinetics and pharmacodynamics at varying doses.

**Phase 2.** Human trials generally involving up to a few hundred participants with the condition intended to be treated; designed to assess the safety and efficacy of a new drug and, like phase 3 trials, often use surrogate measures.

**Phase 3.** Large-scale human trials generally involving several hundred to several thousand patients that are ideally randomized, controlled, and blinded; intended to form the basis for FDA approval.

**Pivotal trials.** An informal term used to refer to the studies on which the FDA primarily relies in making its approval decision; pivotal trials are usually phase 3 trials, but earlier-phase trials may also serve as the basis for approval at the discretion of the FDA.

**Postmarket requirements (PMRs).** A clinical trial or other study an applicant is required to conduct after approval.

**Postmarket commitments (PMCs).** A clinical trial or other study an applicant agrees with the FDA to conduct after approval.

**Prescription Drug User Fee Act (1992).** US legislation authorizing the FDA to collect "user fees" from drug manufacturers to help fund FDA drug review activities; later expanded to medical devices, generic drugs, and biosimilar products.

**Right-to-try laws.** State or federal laws that facilitate access to experimental therapies outside of clinical trials and with limited FDA oversight.

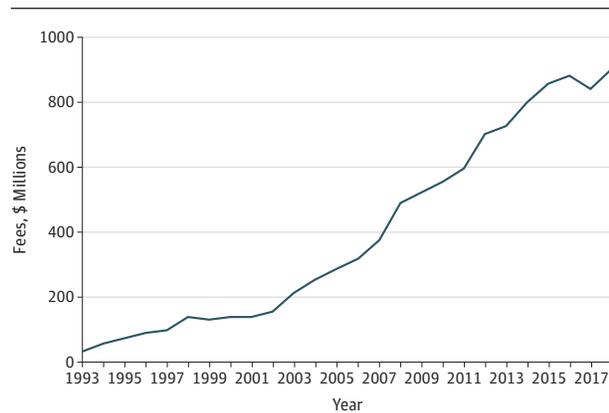
**Risk Evaluation and Mitigation Strategies (REMS).** A program created in 2007 that authorizes the FDA to restrict the distribution of high-risk new drugs to certain facilities or health care providers, or to take other measures to ensure that the benefits of a new drug outweigh its risks.

**Sentinel Initiative.** An FDA program created in 2007 that uses electronic health data, including insurance claims data, to engage in active postmarket surveillance and risk identification.

Abbreviation: FDA, US Food and Drug Administration.

controls, randomization, and clinical end points, but they might omit any or all of these study components. They are intended to provide sufficient evidence of the benefit-risk relationship of the drug to obtain FDA approval.<sup>16</sup> In some cases, phase 2 trials can serve as such "pivotal trials," an informal term describing studies used by the FDA to make an approval decision.

Evidence generated during these clinical trials is added to pre-clinical information and submitted as an NDA to the FDA, which evaluates whether the trials support the manufacturer's efficacy claims and demonstrate that the drug is sufficiently safe given its expected benefits.<sup>17,18</sup> The legally mandated requirement that efficacy claims be supported by "adequate and well-controlled" trials has become more flexible and controversial. For example, while the drug approval statute of 1962 generally required 2 adequate and well-controlled randomized investigations because any single trial could be subject to undetected systematic biases, in 1997 Congress codified the FDA's informal practice of accepting a single clinical trial in

**Figure 2. Fees Collected by the FDA Under the Prescription Drug User Fee Act**

Data are from annual Prescription Drug User Fee Act financial reports (1993-2018) and exclude data from other user fee acts. FDA indicates US Food and Drug Administration.

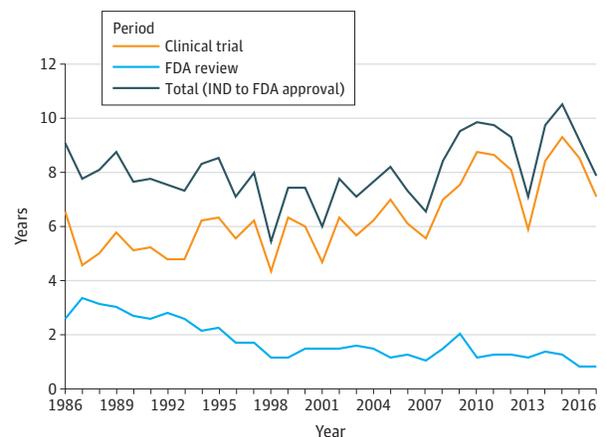
certain circumstances, such as when data from populations other than those currently under study provided additional support or when a multicenter study of excellent design provided highly reliable and statistically strong evidence.

#### Preapproval Testing: Outcomes

The proportion of new drugs supported by at least 2 pivotal trials decreased from 80.6% in 1995-1997 to 52.8% in 2015-2017, based on 124 and 106 approvals, respectively, while the median number of patients did not change significantly (774 vs 816,  $P = .83$ ).<sup>19</sup> Comparing the same 2 periods, the proportion of approvals based on at least 1 pivotal trial that used an active comparator (as opposed to placebo or historical controls) decreased from 44% (177/401) to just 29% (74/253), and the proportion of approvals based on nonrandomized studies with only a single intervention group (ie, not concurrently controlled) increased from 4% (5/124) to 17% (18/106).<sup>19</sup> Over the same time, the length of trials increased: the proportion of approvals based on at least 1 pivotal trial of at least 6 months' duration increased from 26% (32/124) to 46% (49/106).<sup>19</sup>

#### Expanded Access: The Law

Historically, critics who opposed basic preapproval testing have argued that evidence generation delays patient access to some drugs that are eventually proven effective. In response, policies have evolved to provide seriously ill patients with access to unapproved treatments outside of clinical trials. In 1987, as momentum intensified to expedite access, development, and approval during the AIDS epidemic, "expanded access" regulations formalized existing policies allowing patients with serious or life-threatening illnesses to receive experimental substances before FDA approval, provided certain conditions were met. These policies are sometimes referred to as compassionate use programs, but this term is problematic because it may not necessarily be compassionate to provide a patient with access to an untested substance that could confer risks but no benefit. The FDA approves almost all such requests, but access to experimental drugs can be denied by manufacturers, which may be reluctant or unable to make their unproven treatments available at marginal cost and may be concerned about the need to report

**Figure 3. Clinical Trial and FDA Review Periods, 1986-2017**

Clinical trial period data (ie, Investigational New Drug [IND] effective date to New Drug Application [NDA] approval date) available for 65% of products; review period data (ie, NDA approval date to US Food and Drug Administration [FDA] approval) available for 75% of products. IND effective dates and NDA approval dates were obtained from Federal Register patent term restoration notices and FDA approval documents. If no effective date was provided, the effective date was presumed to be 30 days after the IND submission date.

any adverse events to the FDA.<sup>20</sup> State and federal "right-to-try" laws enacted since 2014 attempted to broaden this approach in a way that would minimize or eliminate the FDA's involvement. However, given the flexible expanded access program already available under FDA regulations, the new laws have had little documented effect.

#### Expanded Access: Outcomes

The number of expanded access requests for individual patients (as opposed to groups) approved by CDER and the Center for Biologics Evaluation and Research (CBER) increased from an annual mean of 1165 in 2010-2013 to 1745 in 2014-2017.<sup>21</sup> The FDA approved such requests about 98% to 99% of the time during 2010-2017, usually within a few days.<sup>22</sup> FDA analysis of expanded access requests from fiscal years 2010 to 2014 found that only 30% of 408 drugs for which expanded access was sought had received agency approval for marketing by September 30, 2015.<sup>23</sup>

#### Expedited Development and Approval: The Law

After the 1962 Drug Amendments, manufacturers and advocacy groups expressed concern that the FDA's heightened data requirements were increasing the time and cost required to obtain approval. In response, Congress and the FDA reduced evidentiary requirements in several ways (Box 2). For example, the Orphan Drug Act of 1983 recognized that "clinical tests for Orphan [rare disease] drugs cannot be conducted under the same requirements as tests for drugs for common diseases."<sup>24</sup> The flexibility that the FDA has since applied to premarket testing requirements for rare-disease drugs, later defined as those addressing conditions affecting fewer than 200 000 people in the United States, has raised concerns about the solidity of the evidence base for some approvals based on nonrandomized trials.<sup>25</sup> In addition to this more flexible approach to evidence generation, the act provided companies with research grants, tax benefits, and 7 years of nonpatent exclusivity (to run concurrently with any patent period) to promote the development of treatments for rare conditions.<sup>26</sup>

Three other programs were developed to reduce the requirements for clinical trial evidence for drugs to be used in serious conditions. A 1988 Fast-Track program codified the FDA's ability to approve drugs on the basis of phase 2 trials alone. In 1992, the Accelerated Approval program made it possible for drugs to be approved based on surrogate measures (such as changes in results of a laboratory test) that were not yet well established but that were seen as "reasonably likely... to predict clinical benefit" (such as myocardial infarction or survival), rather than on a demonstration of an improvement in the clinical end points themselves. This was accompanied by the requirement for completion of postapproval studies to verify and describe the drug's actual clinical benefit. In 2012, Congress added a Breakthrough Therapy program with features and intent similar to the Fast-Track program, but with more formalized internal review processes and a name that for the first time implied a large magnitude of benefit. In a guidance document, the FDA explained that breakthrough-designated drugs may be approved on the basis of "alternative clinical trial designs" that may be smaller and require less time to complete.<sup>27</sup> In addition, in 2016 the 21st Century Cures Act mandated that the FDA "maximize" use of such measures in the approval of new drugs<sup>28</sup>—a recommendation that is having a profound effect on approval standards by encouraging the use of imaging or laboratory studies to form the basis of efficacy determinations.

### Expedited Development and Approval: Outcomes

The proportion of drugs approved with an Orphan Drug Act designation increased from 18% (55/304) in 1984-1995, to 22% (82/379) in 1996-2007, to 41% (154/380) in 2008-2018. Compared with trials for drugs to treat common diseases, trials of drugs for rare diseases have been smaller (median, 96 vs 290 participants), less likely to be randomized (30% vs 80%) or double-blinded (4% vs 33%), and more likely to assess disease response (68% vs 27%) rather than overall survival (8% vs 27%).<sup>25</sup> The number of new medications qualifying under the Orphan Drug Act is likely to increase further because of developments in genomics research that divide common diseases (such as breast or lung cancer) into genetic subtypes that can occur in fewer than 200 000 people in the United States.

The proportion of approved drugs that qualified for Fast-Track designation likewise increased from 11% (37/328) in 1989-1998, to 18% (49/265) in 1999-2008, to 34% (121/356) in 2009-2018 (Figure 4). Similarly, the proportion of approved drugs that qualified for Accelerated Approval averaged 9% (28/313) from 1993-2001, 11% (23/217) from 2002-2010, and 13% (39/309) from 2011-2018. The first breakthrough-designated drugs were approved late in 2013, and 27% (57/213) of new drugs approved between 2014 and 2018 were granted a breakthrough designation.<sup>29</sup> The Breakthrough Therapy program led to substantially shorter total development times (4.8 vs 8.0 years), has proven popular among drug sponsors,<sup>30</sup> and has been misinterpreted by physicians as implying higher levels of efficacy than has necessarily been demonstrated.<sup>31</sup> One study found that 52% (16/31) of all breakthrough-designated drugs approved between 2013 and 2016 were approved on the basis of phase 1 or phase 2 trials, 45% (14/31) on the basis of a single trial, and 42% (13/31) without using either an active or a placebo control.<sup>29</sup> These figures were substantially higher for oncology drugs. However, a follow-up study of 33 breakthrough and 25 nonbreakthrough cancer medicines approved between 2012 and 2017 found

### Box 2. Special Approval Programs

**Orphan Drug Act (1983).** US legislation creating incentives for the development of rare disease treatments, defined in 1984 as diseases or conditions affecting fewer than 200 000 people in the United States.

**Fast-Track (1987).** A program intended to expedite the development, evaluation, and marketing of new therapies for serious and life-threatening conditions by, among other things, eliminating phase 3 trials.

**Accelerated approval (1992).** A program intended to expedite the development and marketing of new therapies for serious and life-threatening conditions by allowing the use of surrogate measures only reasonably likely to predict clinical benefit as end points for the pivotal clinical trials forming the basis for drug approval.

**Priority review (1992).** Under the Prescription Drug User Fee Act, the FDA committed to first-cycle review deadlines for new drug applications of 6 months for priority applications and 12 months for standard applications (shortened to 10 months by 2002).

**Breakthrough Therapy (2012).** Experimental therapies designated in this program are eligible for greater FDA attention and expedited response timelines during the clinical development process.

Abbreviation: FDA, US Food and Drug Administration.

no statistically significant differences in response rates for solid tumors compared with nonbreakthrough products (37% vs 39%), nor in novel mechanisms of action (36% vs 39%), rates of death (6% vs 4%), or serious adverse events (38% vs 36%).<sup>32</sup>

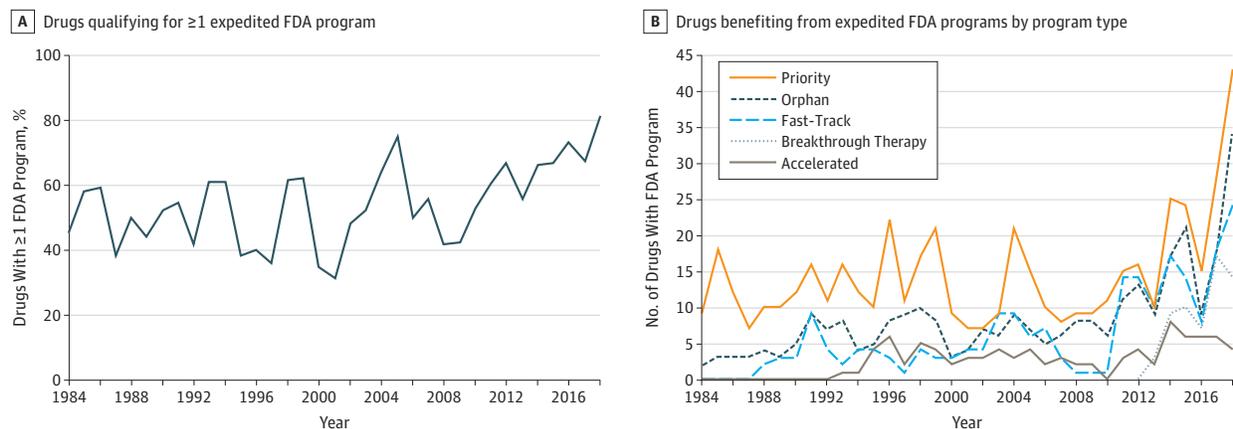
Use of these FDA programs has increased over time as programs have been added and as sponsors have embraced them with increasing frequency. Forty-eight percent of drugs (150/313) qualified for at least 1 expedited program from 1986-1996, 51% (163/319) from 1997-2007, and 64% (243/380) from 2008-2018 (Figure 4).

### Generic Drugs

The "adequate and well-controlled investigations" required by the 1962 Drug Amendments made it more likely that new drugs would be effective and reasonably safe but imposed increased costs on pharmaceutical manufacturers. While manufacturers of brand-name drugs aimed to recoup these costs during temporary exclusivity periods, manufacturers of generic drugs generally could not afford to repeat these clinical trials, and such duplication would have been wasteful. In 1970, the FDA began to allow the submission of Abbreviated New Drug Applications (ANDAs) for generic versions of drugs approved before 1962 ("pre-1962 drugs").<sup>33</sup> To obtain approval of generic versions of post-1962 drugs, manufacturers could submit "paper NDAs," which were applications that relied in part on published reports from the scientific literature rather than on data contained in the NDA of the brand-name product, possibly supplemented with additional clinical data.<sup>34</sup> However, such published reports were not available for about 85% of all drugs approved after 1962,<sup>35</sup> leaving generic manufacturers without an abbreviated pathway for most of the newest and most lucrative products. As a result, by the early 1980s, about 150 drugs approved after 1962 were off-patent but had no generic equivalents available.<sup>35</sup>

To address this problem, Congress enacted the 1984 Hatch-Waxman Act, which expanded the ANDA pathway to encompass drugs approved after 1962, the patents on which were beginning

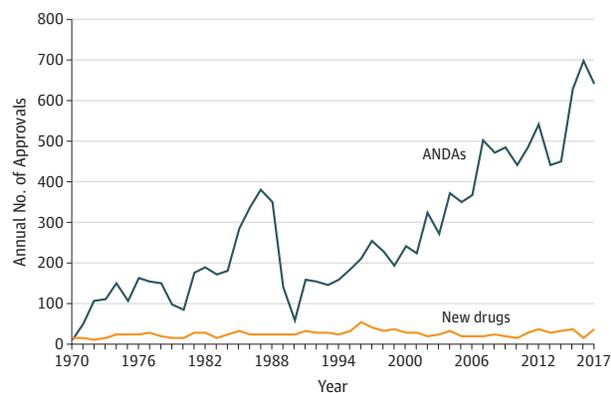
Figure 4. Number of Drugs Benefiting From Expedited Programs, 1984 to 2018



A, Forty-eight percent of drugs (150/313) qualified for at least 1 expedited program from 1986-1996, 51% (163/319) from 1997-2007, and 64% (243/380) from 2008-2018. B, Drugs may benefit from more than 1 program. Before the establishment of the 2-tiered priority review classification system in 1992, the US Food and Drug Administration (FDA) used a 3-tiered classification system. For drugs approved between 1984 and 1992, types A (important therapeutic gain) and B (modest therapeutic gain) were considered to correspond to priority review and type C (little or no therapeutic gain) to standard review.

Drugs were categorized as subpart E (fast-track) drugs using the FDA's annual summaries, other public reports, and information provided by the FDA under the Freedom of Information Act. Accelerated approvals were identified using FDA documents and the FDA's annual summaries of novel new drugs. Drugs were categorized as having an Orphan Drug Act designation using the FDA's monthly drug approval reports database and the FDA's orphan drug database (expanded access not included).

Figure 5. Annual Number of Abbreviated New Drug Applications and New Drug Approvals, 1970 to 2018



"New drugs" include only new molecular entities and exclude biologics, which are not subject to copying via the Abbreviated New Drug Application (ANDA) pathway. ANDAs include discontinued ANDAs and exclude tentative approvals and approvals with over-the-counter status. Years indicated are calendar years. The surge in ANDA approvals from 1985 to 1988 followed the enactment of the 1984 Hatch-Waxman Act. ANDA approvals prior to the Hatch-Waxman Act occurred pursuant to US Food and Drug Administration regulation.<sup>40</sup> Sources: drugs@FDA downloadable data files and Darrow and Kesselheim.<sup>41,42</sup>

to expire in larger numbers.<sup>36</sup> The law provided that a generic drug could be approved if pharmacokinetic testing showed that the generic drug achieved blood levels comparable to those of its reference product (bioequivalence), without the need to independently demonstrate its own clinical outcomes.<sup>37,38</sup> In addition to meeting technical bioequivalence standards, generic drugs had to be identical in active ingredient, strength, dosage form, and route of administration but could differ in certain respects, such as inactive ingredients and appearance.<sup>39</sup>

The ANDA pathway has been widely used, with the number of generic drugs approved annually increasing from a median of 136 from 1970-1984, 284 from 1985-2012, and 588 from 2013-2018. Over the same period, the annual number of new drugs on which generic manufacturers could rely to produce ANDA products has changed little (Figure 5). The proportion of prescriptions filled with generic drugs has also increased substantially, from approximately 9% in 1970<sup>43</sup> to 43% in 1996,<sup>44</sup> to 90% in 2017.<sup>45</sup> Despite this growth, generic drugs represent just 22% of drug expenditures.<sup>46</sup> It has been estimated that the sharply increased use of generic drugs has saved the US health care system more than \$1 trillion in the last 10 years.<sup>46</sup>

### Biosimilar Biologics

The ANDA provisions of the Hatch-Waxman Act did not explicitly address biologics, which are generally therapeutic proteins made from living cells. Few of these existed in 1984, and the FDA later determined that the ANDA process could not be used to approve copies of biologics approved under a BLA.<sup>47</sup> However, biologics currently account for an increasing proportion of clinically important drugs (representing 29% of new drug approvals in 2018), as well as of the total pharmaceutical budget.<sup>48</sup> As a result, as more high-cost biologics such as monoclonal antibodies were approved by the FDA and as patents on those products began to reach their expiration dates, the absence of a follow-on biologics pathway began to take on greater importance. In 2010, Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) as part of the Affordable Care Act. The act authorized an abbreviated pathway for so-called biosimilars. This term is used because given the complexity of these large, cell-manufactured proteins, it is considered impossible for other companies to produce an identical version—just a similar one. Notwithstanding any biochemical or conformational differences, biosimilars must have "no clinically meaningful differences... in terms

of... safety, purity, and potency” compared with the original medication.<sup>49,50</sup>

The FDA approved only 73 biologics between 1984 and 2009,<sup>41,51</sup> and few were off-patent when the BPCIA took effect. Several of these were follow-on biologics, such as alglucosidase alfa (Myozyme [2006]; Lumizyme [2010]), approved via the regular, nonabbreviated drug approval pathway.<sup>35</sup> The first true biosimilar approved under the BPCIA, the colony-stimulating factor filgrastim-sndz (Zarxio), was approved in 2015, 3 years after the FDA issued draft biosimilar guidance. Through June 2019, the FDA had approved 20 biosimilars for 9 distinct drug products,<sup>52</sup> some of which have not yet entered the market because of ongoing patent disputes or settlements. The number of US biosimilar approvals has increased each year since 2015 (1 in 2015; 3 in 2016; 5 in 2017; 7 in 2018), but the number of branded biologics with approved biosimilars in the US market (9 drugs) remains less than in Europe (16 drugs), where approval procedures for biosimilar products was created in 2003.<sup>51</sup>

### Approval Period

#### Drug Approval Trends

Since 1986, the mean annual number of new drug approvals, including biologics, was 34 from 1990-1999, 25 from 2000-2009, and 41 from 2010-2018. The peak in 1996 is generally attributed to the FDA's hiring of additional review personnel enabled by funds provided under the 1992 PDUFA. Twenty-one therapeutic biologics were approved by CDER (excluding biosimilars and including those transferred from CBER to CDER in 2003<sup>53</sup>) from 1986-1996, 44 from 1997-2007, and 88 from 2008-2018. Forty-two vaccines were approved from 1998 to 2018, reflecting an annual mean of 2.0 approvals from 1998-2008, and 1.8 approvals from 2009-2018. The annual numbers of drug, biologic, and vaccine approvals are shown in Figure 6.

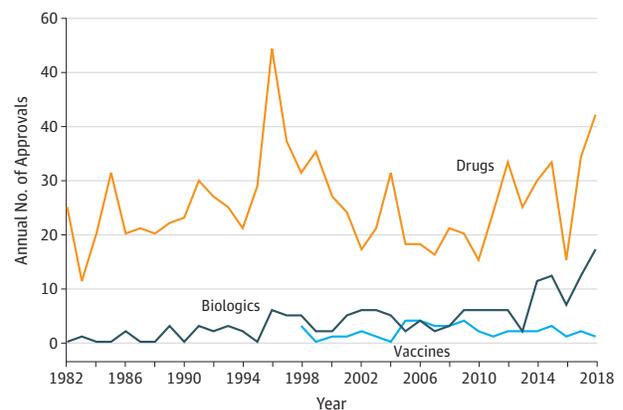
#### Market Exclusivity Periods: The Law

The high prices of newly approved prescription drugs are made possible in part by patents, which confer a temporary legal right to exclude others from making, using, selling, or importing an invention. The concept of exclusive rights to inventions was created centuries ago, and the United States enacted a federal patent law in 1790.<sup>56</sup> This patent law was originally intended as a means of incentivizing scientific progress; when exclusivity expired, other manufacturers could begin producing an invention, leading to lower prices, and the patent holder would be motivated to invent new products to maintain and increase profits.

However, in the case of US pharmaceuticals, this approach does not always operate as envisioned. This is partly because it is sometimes difficult to ascertain the value of a new product compared with that of its predecessor, causing some patients and clinicians to embrace heavily promoted, newly patented variations that may contribute little additional therapeutic value.<sup>57</sup> Insurance coverage of such patented but low-value drugs has allowed drug prices to increase by propping up sales volume, even after patents expire.<sup>58,59</sup> In the US setting—unlike in most other developed countries—government price negotiation is limited.

Patent applications on active ingredients are also generally filed early in the drug development process, so that heightened clinical trial and approval requirements after 1962 reduced the average pat-

Figure 6. Annual Number of Drug, Biologic, Device, and Vaccine Approvals

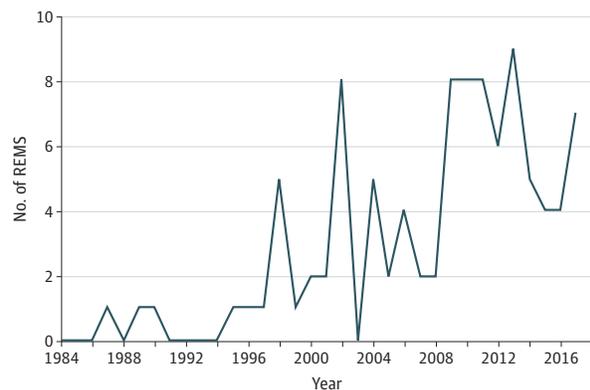


“Drugs” excludes biologics and vaccines. “Biologics” excludes vaccines. Data on the number of drugs, biologics, and Abbreviated New Drug Applications (ANDAs) approved by the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research between 1982 and 2018 were obtained from the FDA.<sup>41,42,54</sup> Vaccine approval information was obtained from current and archived approval lists of the FDA's Center for Biologics Evaluation and Research, which were available beginning in 1998.<sup>55</sup> Vaccine approvals before 1998 and nonvaccine products approved by CBER at any time (except those transferred to CDER in 2003) were not included. The peak of new drugs in 1996 is generally attributed to the FDA's hiring of additional review personnel enabled by funds provided under the 1992 Prescription Drug User User Fee Act.

ent term remaining after approval from 13.8 years in 1966 to 8.9 years in 1977.<sup>60,61</sup> To compensate for lost patent exclusivity, the Hatch-Waxman Act granted brand-name manufacturers “patent term restoration,” an opportunity to extend 1 patent per drug by up to 5 years, so long as the total time from initial FDA drug approval to patent expiration did not exceed 14 years.<sup>36</sup>

The Hatch-Waxman Act also created exclusivities separate from patent rights, similar to the 7-year Orphan Drug Act exclusivity for drugs for rare diseases. The most important of these prevents a competitor from filing a generic drug application until at least 4 years after a new chemical entity is approved.<sup>62</sup> Additional exclusivities have since been added. In 1997, after companies proved unwilling to voluntarily test their products in children if there was no specific pediatric indication, Congress authorized a 6-month extension of exclusivity to companies that agreed to study their drug products in children if requested by the FDA. The BPCIA created 12 years of exclusivity for biologics, to run concurrently with any patent-based exclusivity. In 2012, the Generating Antibiotic Incentives Now (GAIN) Act authorized 5-year extensions of nonpatent exclusivity to incentivize the development of certain new antibacterial and antifungal drugs, added to the end of the periods under the Hatch-Waxman and Orphan Drug Acts.<sup>63</sup> Because these exclusivities (except for 6-month extensions) run concurrently with any patent terms, the average exclusivity period before generic entry has remained approximately 13.5 years since the 1990s.<sup>64</sup> Nevertheless, manufacturers have been successful in influencing the health care system to use single-enantiomer versions of racemic products,<sup>65,66</sup> newly patented fixed-dose combination drugs,<sup>67</sup> drug-device combinations,<sup>68</sup> or other slight modifications that are eligible for new patents that extend years beyond the original patent's expiration,<sup>69</sup> even after the underlying drugs have long since become available as low-cost generics.

Figure 7. Risk Evaluation and Mitigation Strategies With Elements to Ensure Safe Use, by Year of Drug Approval



Source: US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) data files. A REMS was applied to 1 drug approved before 1984 (methadone [Dolophine], 1947).

### Extended Exclusivity Periods: Outcomes

A review of 170 top-selling drugs with market exclusivity that expired in 2000–2012 found that 83 (49%) benefited from patent term restoration, which accounted for a median extension of 2.75 years.<sup>70</sup> From 2012 to 2017, the FDA awarded 12 products an additional 5 years of exclusivity under the GAIN Act.<sup>71</sup> From 1998 through 2018, 242 grants of 6-month pediatric exclusivity were awarded.<sup>72</sup> The clinical trials supporting pediatric exclusivity extensions often cost manufacturers far less than the additional revenues earned because of the extension of exclusivity; 1 study found median trial costs to be \$36.4 million, compared with median resulting revenue benefits of \$221.7 million.<sup>73</sup> Including patent extensions and all nonpatent exclusivities, generic entry for small-molecule drugs continues to occur on average approximately 13.5 years after FDA approval.<sup>64</sup>

### Postapproval

The clinical outcomes associated with a new drug used in typical patient populations cannot be defined completely by preapproval testing. This is especially true for adverse events, but is also an issue for understanding the magnitude and frequency of beneficial outcomes when a drug is used by typical prescribers and patients, rather than the less representative populations often studied in clinical trials. Thus, the FDA's evaluation of safety and efficacy at the time of a drug's initial approval is increasingly subject to refinement based on data from postapproval use in routine settings as well as from required postapproval studies. This information can come from a number of sources.

#### Postapproval Testing

Sponsors of drugs approved under the Accelerated Approval program are obliged by law to engage in postapproval study to verify and describe the drug's clinical benefit.<sup>74,75</sup> Under the 2003 Pediatric Research Equity Act, the FDA may require postmarket pediatric studies for drugs with new active ingredients, indications, or dosage forms.<sup>76</sup> Studies imposed by statute or regulation are known as postmarketing requirements. In addition, a manufacturer may prom-

ise to conduct studies known as "postmarketing commitments" to obtain FDA approval.<sup>77</sup>

Because the FDA's influence is weaker after a drug has been approved, the rate of completion of these studies is inadequate. FDA regulations require annual reporting on the status of postmarketing requirements and commitments,<sup>78</sup> and the FDA releases annual status summaries of those that are open and those that were closed within the previous 12 months. However, because some requirements and commitments may be delayed or never completed, these reports tend to indicate completion rates that are higher than when reported by cohort year of approval (or of establishment if after approval). For example, FDA data on postmarketing requirements and commitments that were closed in 2016 indicate that 72% (126/174) of postmarketing requirements and 82% (44/54) of postmarketing commitments were fulfilled, but this was based on an analysis of closed studies.<sup>79</sup> By contrast, a study of 614 postapproval requirements and commitments imposed in 2009 and 2010 found that by the end of 2015, 20% (125/614) had not been started, 25% (156/614) were delayed or ongoing, and only 54% (333/614) were completed.<sup>80</sup>

### Risk Evaluation and Mitigation Strategies

Although Congress gradually expanded the FDA's authority to regulate drugs throughout the 20th century, it sought to avoid authorizing the FDA to engage in activities that could be construed as regulating the practice of medicine. But the distinction between the practice of medicine and the regulation of drugs can sometimes be unclear. For example, the safety or efficacy of a given drug may depend on how it is used by a prescriber or patient, such as when a drug is used off-label or in conjunction with other medicines.

To facilitate approval of high-risk drugs that could nevertheless offer benefit if used properly, the 2007 FDA Amendments Act granted the FDA the authority to require Risk Evaluation and Mitigation Strategies (REMS). These strategies may be required as a condition of approval or for an already approved drug, can apply to both brand name and generic drugs, and may involve (1) a medication guide, used to communicate risk information to consumers; (2) a communication plan to transmit important information to health care practitioners; and (3) elements to ensure safe use, such as requiring patients to enroll in a registry or health care practitioners or pharmacists to obtain special certification (Figure 7).<sup>81-83</sup>

REMS have served to limit overall prescribing, risky prescribing, and off-label prescribing.<sup>84</sup> For example, implementation of a REMS in 2011 for transmucosal immediate-release fentanyl products was followed by a decrease in outpatient dispensing from an estimated 14 400 patients receiving these products in 2012 to 4700 receiving them in 2017.<sup>85</sup> However, frequent off-label use of these highly addictive opioids continued, raising concerns about the effectiveness of the REMS in ensuring appropriate prescribing.<sup>86</sup> Rates of opioid-related deaths declined after a separate REMS was initiated in 2012 for extended release and long-acting opioid analgesics, but the declines were not significantly different from comparison group declines.<sup>87</sup>

### Active Postmarket Monitoring

After approval, drugs are prescribed by typical physicians caring for typical patients in routine clinical practice—circumstances that often differ from those in the trials on which approval is originally based.

In such clinical settings, factors such as patient comorbidities and polypharmacy can result in effectiveness and safety that may differ from the outcomes observed in the preapproval trial environment. Rare adverse events that are difficult to detect in preapproval trials may also become apparent. In 2004, rofecoxib (Vioxx) was withdrawn by its manufacturer after 5 years on the market when postapproval data generated to support a different indication demonstrated the drug increased the risk of myocardial infarction from approximately 1 in 1000 to as much as 4 in 1000.<sup>88-90</sup> This prompted Congress to ask why the FDA had no effective mechanism in place to detect such risks proactively.

The 2007 FDA Amendments Act directed the FDA to establish a system to conduct active postmarket risk surveillance by linking and analyzing safety data using the records of at least 100 million patients aggregated from multiple sources, such as Medicare data, Veterans Affairs data, and private health insurance claims data.<sup>91</sup> The FDA's resulting Sentinel Initiative is in place today and serves as a means of using observational data to detect potential adverse drug effects in typical populations of patients.<sup>92</sup>

## Discussion

The Kefauver-Harris Drug Amendments in 1962 prevented manufacturers from selling a new drug until the FDA reviewed the manufacturer's safety and efficacy data and approved the product for marketing. In response, the pharmaceutical industry and some patient groups urged Congress and the FDA to increase financial incentives and to reduce development and approval times by augmenting FDA review resources and loosening preapproved requirements.

Additional exclusivity rights, which strengthened and sometimes extended the length of a company's monopoly on a given medication, were added to reward the development of rare-disease drugs (1983, 7-year), new drugs (1984, 4- to 5-year), modifications to existing drugs (1984, 3-year), pediatric research (1997, 6-month), biologics (2010, 12-year), and certain antibacterials and antifungals (2012, 5-year). FDA regulations enacted in 1970 and the 1984 Hatch-Waxman Act introduced flexibilities for the approval of generic drugs, which had not been exempted from the 1962 requirements. Between 1983 and 2012, the Orphan, Fast-Track, Accelerated Approval, Priority Review, and Breakthrough Therapy programs sought to accelerate drug availability by formalizing an increasingly flexible interpretation of the 1962 requirement for "adequate and well-controlled investigations" to prove a drug's efficacy.

The number of generic drugs approved has increased to more than 700 per year. Although the number of new drug approvals has remained at or below 60 per year, the proportion of drugs approved using at least 1 special review program increased substantially over time, exceeding 80% in 2018. More than half of the 59 new drugs approved in 2018 received Orphan designation (34 [58%]) and Priority Review (43 [73%]), while the Fast-Track (24 [41%]) and Breakthrough Therapy programs (14 [24%]) were also frequently used. To fund approval activities, user fee payments from the drug industry expanded from \$330 million in 1993-1997 to \$4.1 billion in 2013-2017, as fee amounts increased and the types of products subject to fees were broadened.

Expedited approval programs create substantial administrative costs<sup>93</sup> and allow the approval of new drugs based on fewer,

smaller, and/or earlier-stage clinical trials that may not be randomized, controlled, blinded, or based on traditional measures of how a patient feels, functions, or survives. In addition, the legal standard for approval requires only that a new drug "have the effect it purports or is represented to have" and in general does not require a drug to exceed any particular threshold of efficacy other than zero.<sup>57</sup> Although this statutory language has not changed,<sup>94</sup> expedited programs have reduced the amount and quality of evidence needed to meet the statutory standard.<sup>29,95</sup>

Surrogate measures, including well-established surrogates, have been increasingly used to approve new drugs. A review of pivotal efficacy trials (n = 448) for new drug approvals from 2005-2012 found that 44.3% were based on surrogate measures,<sup>96</sup> while for new drugs approved from 2015-2017 (n = 253), the number was 59.3%.<sup>19</sup> Surrogate measures that have been determined to be "well established" include laboratory tests such as glycosylated hemoglobin level for diabetes medications or low-density lipoprotein cholesterol level for lipid-lowering medications, or pulmonary function tests such as forced expiratory volume in 1 second for cystic fibrosis medications, even though concerns have been raised about the clinical relevance of the first and last of these for specific outcomes. Under the Accelerated Approval program, use of surrogate measures that are not yet designated as well established increased from 9% (28/313) in 1993-2001 to 13% (39/309) in 2011-2018. When these measures do reliably predict how a patient feels, functions, or survives, their use to approve new drugs can accelerate the availability of useful medications. By contrast, a surrogate measure that does not predict actual patient benefit may accelerate approval of a drug that presents risk but could be of little clinical use.

Pressure from patients to make drugs available more quickly and from manufacturers wanting to recoup their development costs has contributed to the increasing use of surrogate measures,<sup>95</sup> and such use has been interpreted to be consistent with the law: "clinical" as used in the FDA's governing statute formally refers to human (non-animal) trials<sup>97</sup> and not to the type of trial end point.<sup>57</sup> This formal definition, however, is in tension with the traditional perception of effectiveness and clinical benefit as referring to how a patient feels, functions, or survives,<sup>27,98</sup> such as the resolution of an infection by an antibiotic, the management of schizophrenic symptoms by an antipsychotic medication, or the achievement of an extended life span with the use of a new drug to treat cancer.

Despite the accumulation of expedited programs that have reduced FDA review times, overall clinical development times have not become shorter (Figure 3), although it is not possible to know what role these programs may have played in preventing an increase in development times. The resistance of total development times to efforts to shorten them could be the result of more submissions of applications for rare disease drugs,<sup>99</sup> which can sometimes pose trial recruitment challenges; a shifting emphasis to more challenging therapeutic categories, such as central nervous system disorder treatments<sup>100</sup>; longer time horizons needed to establish efficacy when early intervention is important (eg, cancer); or other factors.

The effect of the expanding toolbox of FDA programs on the number of new drug approvals or therapeutic value is unclear. Except for biologics, which are still not numerous, and generic drugs, the number of new drug approvals has not increased substantially over the past 3 decades. Although the FDA has on average applied its expedited programs to drugs offering larger health gains,<sup>101</sup>

it is difficult to assess whether these programs have incentivized greater therapeutic innovation or merely allowed more appropriate agency prioritization.<sup>32,69</sup>

In part because of the 1962 Drug Amendments, which required demonstration of efficacy and more rigorous assessment of adverse events before marketing, FDA approval of drugs is highly respected around the world. However, as its regulatory standards and approval come to rely on less substantial evidence, the benefits of earlier access must be weighed against the possibility that patients will be exposed to drugs with benefit-risk profiles that may turn out to be less favorable than expected or for which clinical benefit is never confirmed.<sup>102</sup> These concerns may be exacerbated when patients who participate in clinical trials are different than those who receive the drugs in the clinical setting. Although new treatments provide patients with additional therapeutic options, problems can result if promotion causes new drugs approved on the basis of limited evidence to be used in patients for whom there is less evidence of benefit or to displace established treatments that have better-characterized risk profiles with comparable or better-proven effectiveness. Because new treatments tend to be more expensive than older ones, these market imperfections can contribute to expenditures that may not be justified by increased therapeutic benefit.

Achieving the proper balance between speed of development and rigorous evidence generation requires careful construction of regulatory requirements, proper execution of these rules, and evidence-based evaluation of whether new programs are truly benefiting the public. Despite the political popularity and perceived success of many of the programs implemented since the 1980s, the facilitated review processes they made possible appear to have led to both the benefits of earlier access, as well as the potential disadvantages of rapid approval of treatments with clinical outcomes that are not adequately characterized. Congress, the research community, or both should periodically reevaluate the balance between these consequences. More evidence is also needed on the extent

to which these programs may impose administrative burdens that are not justified by their benefits, encourage unproductive regulatory maneuvering and competition over the FDA's limited resources, or focus attention on easily measurable but less relevant metrics, such as approval speed or number of new drugs. The test of whether the drug approval framework is successful ultimately turns on the extent to which those drugs contribute to or detract from patient well-being, including the effects of high drug costs. Ideally, regulatory and incentive structures should be based on quantifiable measures of actual patient-relevant therapeutic benefit, and these measures should be communicated clearly and objectively.

### Limitations

This review has several limitations. First, despite the observation that the number of new drugs has not increased substantially and overall development times have not decreased substantially, it is not possible to know whether these measures would have been less favorable in the absence of new laws, programs, and incentives—particularly in light of the substantially increasing complexity of new pharmacological interventions. Second, magnitude of clinical benefit is difficult to compare across different indications and populations, and data were not available to quantify trends across all drugs.

### Conclusions

Over the last 4 decades, the approval and regulation processes for pharmaceutical agents have evolved and increased in complexity as special programs have been added and as the use of surrogate measures has been encouraged. The FDA funding needed to implement and manage these programs has been addressed by expanding industry-paid user fees. The FDA has increasingly accepted less data and more surrogate measures, and has shortened its review times.

#### ARTICLE INFORMATION

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**Concept and design:** All authors.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Darrow.

**Critical revision of the manuscript for important intellectual content:** All authors.

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