

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Mary Beth Hamel, M.D., M.P.H., *Editor***Speed, Safety, and Industry Funding —
From PDUFA I to PDUFA VI**Jonathan J. Darrow, S.J.D., J.D., M.B.A., Jerry Avorn, M.D.,
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In August, President Donald Trump signed into law the sixth version of key legislation for the Food and Drug Administration (FDA), known as the Prescription Drug User Fee Act (PDUFA VI). The legislation continues a policy that authorizes the agency to collect user fees from pharmaceutical companies, providing funds that the FDA uses to hire additional staff to review new drug products and thereby reduce approval times. PDUFA VI is part of the FDA Reauthorization Act of 2017 (FDARA),¹ which also renewed similar user-fee programs for medical devices, generic drugs, and biosimilars.

User fees emerged after the growing AIDS crisis of the 1980s and early 1990s, when concern mounted that regulatory delays — caused in large part by inadequate public funding that did not allow the FDA to hire sufficient personnel — were slowing the approval of promising new treatments. In the face of this persistent financial shortfall, the pharmaceutical industry stepped forward to offer funding in the form of “user fees,” in exchange for FDA commitments to accelerate drug review. From the beginning, some policymakers and patient advocates argued that although user fees could help the FDA carry out some of its statutory functions, the funding could create an uncomfortable dependence of the FDA on the industry it regulates.²⁻⁵

As the FDA prepares to implement FDARA, we trace the evolution of the key provisions of the law — which affect the funding of the FDA and the timeliness and safety of the products it approves — from its inception in 1992 to the present, including a review of the major user-fee provisions of the new law. We then consider the effect

of user-fee legislation on FDA operations and the legislative process.

EXPANDING FEES AND FDA
COMMITMENTS, SHRINKING
REVIEW TIMES

Starting in 1962, the FDA required that manufacturers conduct clinical trials to demonstrate the efficacy and safety of an investigational drug before its approval^{6,7} — a major new requirement created in the wake of the thalidomide disaster. As Congress increased the oversight responsibilities of the FDA without commensurate increases in funding,^{8,9} the average time it took the FDA to review a new drug application swelled from 14 months in 1963 to more than 35 months by 1979.^{10,11} Complaints from the pharmaceutical industry and patient-advocacy groups led to the first enactment of PDUFA in 1992 to help the FDA address this problem.

PDUFA I authorized the collection of three types of fees. A fee of \$100,000 was to be collected with most new drug applications. To ensure funding stability notwithstanding fluctuations in the number of applications, annual establishment fees (\$60,000) and product fees (\$6,000) were to be paid for each manufacturing facility and manufactured drug, respectively.⁵ Fee amounts increased annually over a period of 5 years according to a statutory schedule, with additional upward adjustment for inflation. Smaller companies paid 50% of the application fee, and the FDA could waive or reduce fees if necessary to protect public health.

In return for paying user fees, the pharma-

ceutical industry received several explicit assurances. To prevent the fees from being diverted to other regulatory purposes, PDUFA required that they be used only for expediting the review of human drug applications. The most important assurances, however, were performance goals set forth in “commitment letters” that required the FDA to review standard applications within 12 months and priority applications — for drugs determined by the FDA to treat serious or life-threatening conditions that offer improvements in safety or effectiveness — within 6 months.¹²

In 1992, then-FDA Commissioner David Kessler estimated that the user fees would allow the agency to hire 620 new employees to help achieve these goals.¹³ Fees had to be paid equally for standard and priority applications whether or not an application was approved, though approximately 77% of applications were approved during the 1990s, a figure that has since risen to approximately 86%.¹⁴ Staff increases and the proportion of applications reviewed by the deadlines were to be phased in over a period of 5 years, with the aim of hiring all planned staff and reviewing at least 90% of newly submitted applications on schedule by the expiration of PDUFA.

The legislation was written to expire automatically in 1997. Kessler explained that this 5-year sunset provision would provide the opportunity “to see whether we at the Agency are meeting our performance goals and to allow the public, the industry. . . and Congress to decide whether the program should be continued.”¹³ Industry also supported a sunset provision, explaining that if performance goals were not met, it would recommend that the legislation be abolished.⁸ By the end of PDUFA I in 1997, the FDA reported meeting its goal of reviewing 90% of applications submitted in the previous fiscal year within either 6 or 12 months after submission.¹⁵

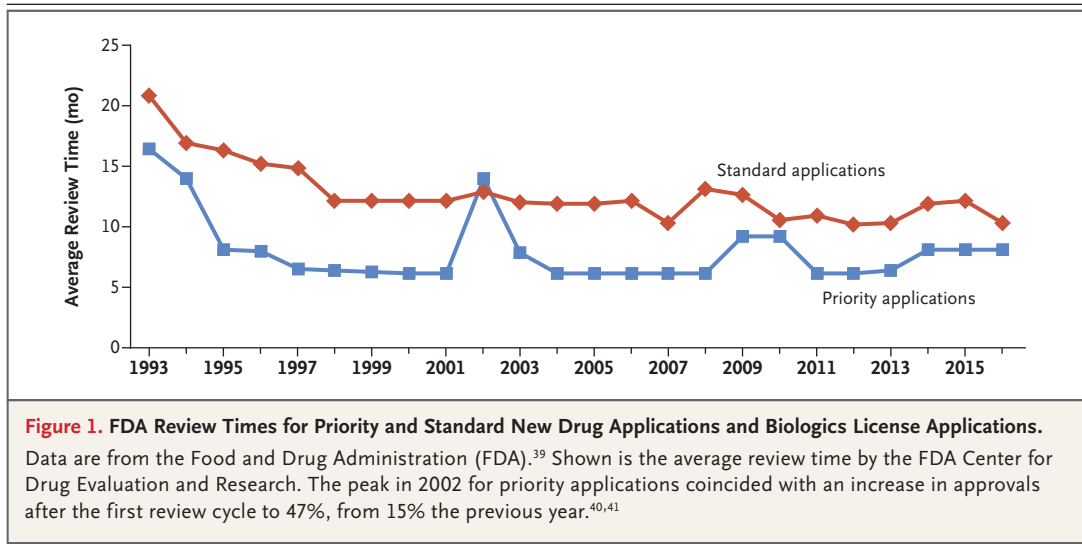
Judging PDUFA a success,¹⁶ Congress reauthorized user fees in 1997, 2002, 2007, and 2012 (PDUFA II to V). PDUFA II phased in a reduction in review times for standard applications from 12 months to 10 months. It also moved beyond speeding the FDA review period and authorized the use of user fees to help shorten the time spent on clinical trials, which averaged approximately 7 years.¹⁷ PDUFA II also created a formal

structure to ensure timely meetings between the FDA and sponsors throughout product development.¹⁷

The initial PDUFA regulations permitted salary support only for FDA staff involved in the drug-approval process, but not for the much smaller FDA program that evaluated drug safety after marketing. That changed with PDUFA III, which in 2002 allowed user fees to be applied to drug-safety studies as well: \$71 million in PDUFA funds over a period of 5 years could be applied to research on postapproval adverse effects.¹⁸ It also required the FDA to consult with stakeholder groups, particularly the pharmaceutical industry, before the next reauthorization.

In 2004, the nonsteroidal antiinflammatory drug rofecoxib (Vioxx) was abruptly removed from the market after 5 years of use by tens of millions of Americans when it was found to substantially increase the risk of cardiovascular events,^{19,20} a risk later determined to also be present for other cyclooxygenase-2 selective drugs, although to a lesser extent.²¹ Public outcry and Congressional hearings focused attention on the fact that the FDA did not have in place a systematic, proactive system for adverse-event surveillance once a drug was on the market, even though the increasing digitization of health care records and modern pharmacoepidemiologic approaches made this quite practical.²² Congress used PDUFA IV (part of the 2007 FDA Amendments Act) as a vehicle to expand funding for such postmarketing surveillance, authorizing additional fee revenues of \$225 million over a period of 5 years to support the drug-safety activities of the FDA.^{23,24}

A major innovation of PDUFA V (part of the 2012 FDA Safety and Innovation Act) was to reduce the number of FDA review cycles. By 2011, approximately 70% of approved drugs were approved after the first review cycle. From the beginning of PDUFA, the FDA has had 60 days after an application is received to assess whether it is complete enough for substantive review, at which time the application is considered to be filed.²⁵ Under PDUFA V, the 6-month and 10-month review periods for new drugs were changed so that this 60-day period no longer counted toward the PDUFA deadlines, providing the agency with additional time to complete the first cycle of review.²⁶ The goal of reducing multicycle reviews was



achieved; within 3 years, the FDA reported that 95% of approved applications were being approved after the first review cycle. Despite the growing emphasis on the need for postapproval safety studies, PDUFA V deleted the provision allocating \$225 million to drug-safety activities.²⁷

To address industry concerns that the agency needed to be more transparent about its expectations and deliberations, PDUFA V obligated the FDA to issue guidance documents and hold public meetings or workshops covering a broad range of topics, including agency–sponsor communication practices, the facilitation of the development of drugs for rare diseases, the determination of when to require a Risk Evaluation and Mitigation Strategy, the Sentinel postmarket surveillance system, and the use of biomarkers in the drug-approval process.

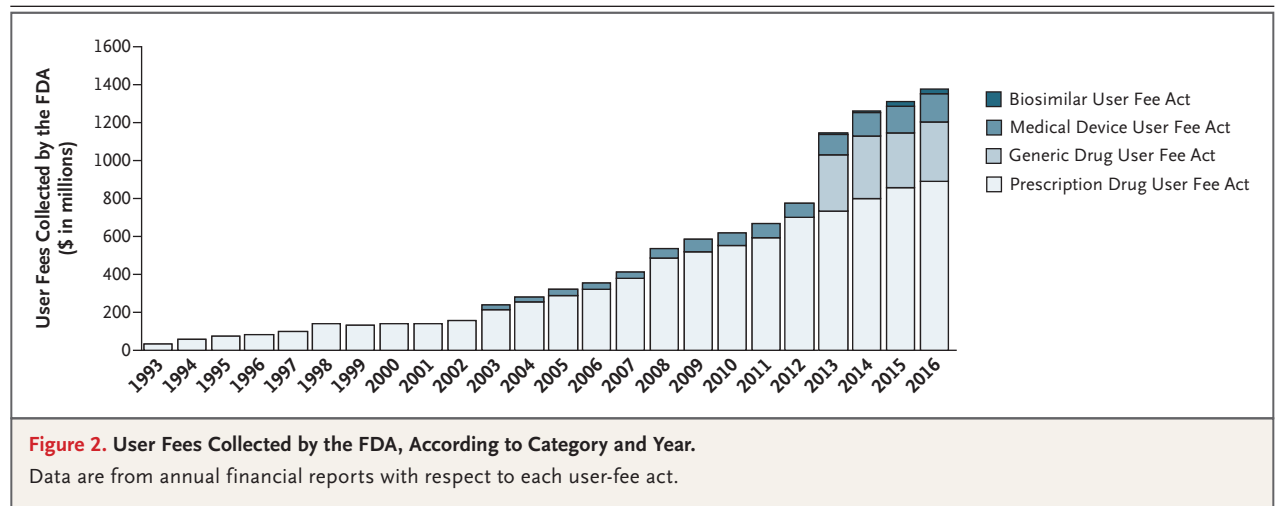
MORE USER FEES FOR OTHER PARTS OF THE FDA

During the discussions leading up to PDUFA I, both legislators and the FDA contemplated the expansion of user fees into other areas, such as medical devices and generic drugs, but those industries either actively opposed the collection of fees or had not yet achieved consensus to support them.^{8,12} As user fees were channeled to statutorily specified drug-review activities, however, it became clearer that the approach could benefit other medical products reviewed by the agency.^{28,29}

After the success of PDUFA, Congress enacted the Medical Device User Fee and Modernization Act (MDUFA) in 2002³⁰ and the Generic Drug User Fee Act (GDUFA) and the Biosimilar User Fee Act (BsUFA) in 2012.²⁷ These acts, modeled on PDUFA, required industry to pay user fees to help speed application reviews, but included some modifications. GDUFA, for example, did not include application-fee waivers or reductions, on the rationale that the majority of generic companies were small and fee amounts were already set at much lower levels than PDUFA fees.³¹ All four programs included detailed performance goals set forth in commitment letters, 5-year sunset provisions, and requirements to negotiate with industry before reauthorization.

FDA REAUTHORIZATION ACT OF 2017

The FDA Reauthorization Act of 2017 amended all four user-fee programs, raising fee-revenue targets for 2018 for drugs (to \$879 million), biosimilars (\$45 million), generic drugs (\$494 million), and devices (\$183 million), with annual increases and adjustments through 2022. Each year the FDA sets user fees to achieve these statutorily prescribed revenue targets. By 2018 the original \$100,000 fee for a new drug application had risen to \$2,421,495.³² New fees were added for generic-drug applications (\$171,823 per drug in 2018), generic-drug manufacturing facilities (\$211,087 per facility annually),³³ medical-device 510(k) pre-



market notification (\$10,566) and premarket authorization (\$310,764) submissions,³⁴ and biosimilar applications (\$1,746,745).³⁵ Other fees also apply, including annual “program fees” of \$304,162 per brand-name drug and \$1,590,792 per generic manufacturer. In some cases, fees may be waived (e.g., for orphan drugs) or discounted, such as for smaller generic-drug companies.

The PDUFA VI commitment letter retained the existing goal of reviewing 90% of priority and standard new drug applications within 6 and 10 months, respectively.³⁶ In analogous letters for the other user-fee acts, the FDA aimed to review 90% of biosimilar applications within 10 months after the 60-day filing date, 90% of priority and standard generic-drug applications within 8 and 10 months, respectively, and 90% of original applications for high-risk medical devices within 180 days if no advisory-committee input is required, or 320 days if such input is required. To facilitate early generic competition, the 2017 law mandated priority review of a proposed generic drug if there are no more than three approved generic products; priority review was already available in the case of drug shortages or for potential first-to-market generic products, including those challenging existing brand-name drug patents.^{37,38}

In its PDUFA VI commitment letter, the FDA agreed to undertake several major initiatives to facilitate drug evaluation and approval. It will expand the Sentinel pharmacovigilance system and hold one or more public workshops to explore the potential use of “real world evidence” not only for safety activities, but also to help support

the approval of new indications or the fulfillment of postapproval study requirements. The FDA also committed to issuing a series of guidance documents relating to greater use of patient and caregiver input in regulatory decision making. Staff will be hired or trained to support the increased use of new biomarkers and surrogate end points, and of adaptive, Bayesian, and other novel clinical-trial designs. Enhanced efforts will be made to further minimize the number of review cycles necessary for approval, including the use of “expedited review” (an internal FDA designation different from priority review or other formal expedited programs) for drugs meeting an important public health need, for which the agency aims to act at least 1 month before the normal PDUFA deadline.

POLICY IMPLICATIONS

PDUFA began in 1992 with the laudable goal of clearing the substantial backlog of investigational drugs that had successfully completed clinical trials but could not be used to treat patients because an underfunded FDA lacked the resources to perform timely reviews of new drug applications. The legislation has generally achieved this goal (Fig. 1).

During the past quarter century, the legislation has expanded substantially in both fee amount and scope (Fig. 2). Net PDUFA fees collected have increased by a factor of more than 30, from approximately \$29 million in 1993 to \$884 million in 2016. Medical-device user fees,

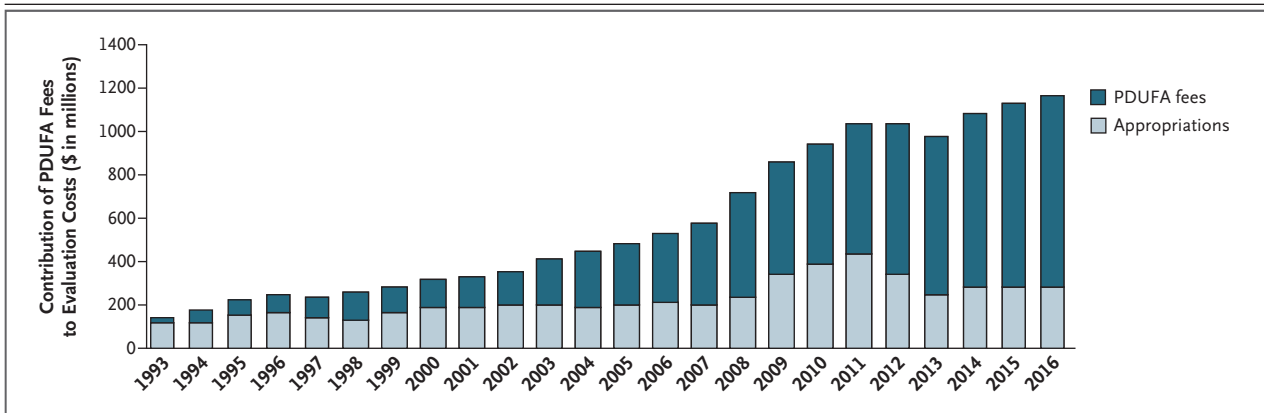


Figure 3. Contribution of Net PDUFA Fees to Total Evaluation Costs of the FDA Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

Data are from annual Prescription Drug User Fee Act (PDUFA) financial reports.

which totaled approximately \$22 million in 2003, rose to approximately \$150 million by 2016. The trend of rapidly increasing fee revenues will continue under the 2017 FDA Reauthorization Act, with base fee amounts for brand-name drugs, devices, generic drugs, and biosimilars rising to a total of approximately \$1.6 billion in 2018, with further fee increases authorized annually through 2022. Between \$8 billion and \$9 billion in industry funding is expected to be transferred to the FDA to meet its salary needs during the 5-year term of FDARA.⁴²

Because of these regulatory changes and the continuing reluctance of Congress to fund FDA staff directly, user fees have risen far faster than the FDA budget. The \$36 million in fees authorized for 1993 constituted approximately 27% of the combined budget of the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.⁴³ By contrast, user fees now make up approximately 75% of FDA scientific review budgets for brand-name drugs⁴⁴ and generic drugs (Fig. 3), as well as substantial portions of its review budgets for medical devices (36%) and biosimilars (29%).^{45,46} Overall, industry-paid user fees (including tobacco, animal-drug, and other user fees) provided approximately 43% of the \$4.8 billion budget of the FDA in 2016 (Fig. 4).⁴⁷ As the proportion of industry funding has increased, so too have the number of FDA employees whose compensation is dependent on such external funding. In May, one Senate sponsor of FDARA cautioned that if

Congress did not move quickly to pass the legislation, layoff notices would have to be sent to more than 5000 FDA employees,^{42,46} far more than the 620 additional employees initially contemplated in 1992.

As industry funding has risen, the extent of statutorily required industry input in the drug-regulation and reauthorization processes has also increased. PDUFA I contained a single reference directing the FDA to consult with industry on the potential establishment of animal-drug user fees.⁴⁸ In 1997, the reauthorization legislation contained a dozen references to consultations with industry, including a provision directing the FDA to consult with industry when developing a plan to ensure compliance by the agency with the legislation.⁴⁹ In 2002, although industry had already been contributing to the development of such legislation since its inception, the reauthorization for the first time required “negotiations” with the industry as part of the next reauthorization process.⁵⁰ Analogous negotiation provisions were included in the medical-device, generic-drug, and biosimilar user-fee enactments in 2002 and 2012. In anticipation of the 2017 legislation, the FDA carried out its statutory obligations to negotiate with manufacturers by holding at least 76 meetings with industry representatives and other stakeholders beginning in 2015. Additional industry and stakeholder meetings were held as part of the MDUFA,⁵¹ GDUFA,⁵² and BsUFA⁵³ reauthorizations.

The centrality of user fees to the modern FDA

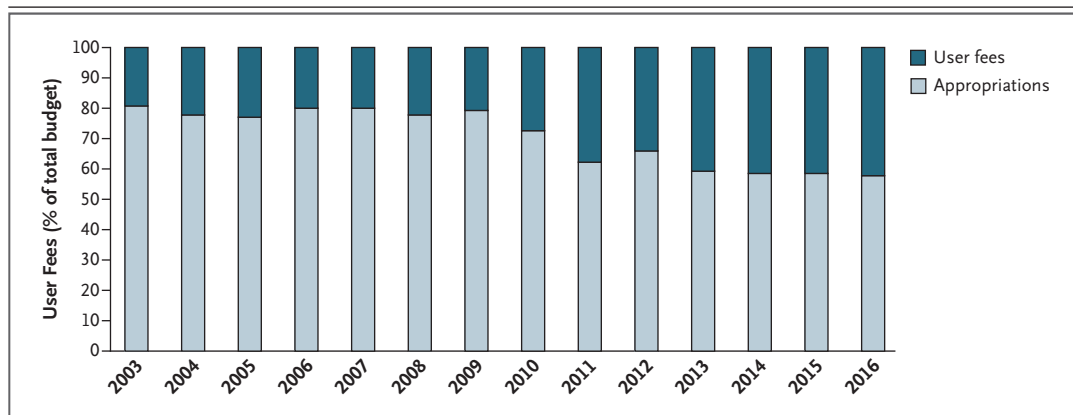


Figure 4. Total User Fees as a Percent of Total FDA Program Budget.

Data are from the FDA annual operating plans (2012–2016 data); 2011 Congressional Justification Executive Summary (2009–2011 data); *FDA FY2009 Appropriations*, Congressional Research Service, November 13, 2008 (2008 data); FDA fiscal year 2007 budget request (2007 data); and FDA fiscal year budgets in brief (2003–2006 data).

has led some observers to express concern that they have contributed to “corrosive capture” of the agency (i.e., a weakening of regulatory independence and of the ability of the agency to uphold traditional efficacy and safety standards) by shaping discourse about how drugs should be regulated or by enabling an unhealthy culture of closeness between the FDA and industry.⁵⁴⁻⁶⁰ Indeed, each successive PDUFA has required the FDA to be increasingly responsive to industry concerns. As part of its commitments in exchange for the provision of user fees by industry, the FDA has established a growing range of deadlines not only for new drug application review but also for proprietary-name review and dispute-resolution procedures, and for various meetings, guidance documents, and communications.³⁶ The FDA has increasingly emphasized “flexibility” in the drug-evaluation process and its criteria for approval, particularly with respect to treatments for rare diseases, a broadening category that constituted 45% of new drugs approved from January 2015 through December 2016. This area is of growing importance in the era of “precision medicine,” in which subtypes of a common condition (e.g., many cancers) can be defined by a specific genotype, making each a rare condition in regulatory terms. For such conditions, the FDA committed to promoting the “innovative use of biomarkers, consideration of non-traditional clinical development programs, . . . evaluation of novel endpoints,” and the “application of new approaches to statis-

tical analysis.”³⁶ For drug evaluation generally, reviewers will be trained regarding the FDA philosophy of timely communication with industry as a “core agency activity.” Recent commitment letters have also expanded the obligations of the FDA to engage outside contractors or consulting firms to assess its programs and performance.

In the face of tightly constrained public funding for FDA staff, user-fee legislation has contributed to the more rapid evaluation and approval of new drugs and funds the generation of important additional evidence after drug approval. Moreover, patient groups have often joined industry in favoring the trade-off inherent in deferring evidence collection to obtain earlier approval, although many patient groups receive funding from industry, creating potential conflicts of interest.^{61,62}

Nevertheless, although industry and public interests sometimes align, they also can be at odds.⁶³⁻⁶⁵ A focus on speed, flexibility, and responsiveness to industry needs may accelerate approval, but it can also increase the chance that a newly marketed drug may not be as effective or safe as traditional standards would have demanded.⁶⁶ This can occur if novel end points or surrogate measures — the latter of which now account for approximately half of all new drug approvals — later prove to correlate poorly with actual clinical outcomes,⁶⁷⁻⁶⁹ if complex statistical analyses or trial designs increase interpretation challenges and opportunities for error,⁷⁰⁻⁷²

or if unanticipated safety concerns emerge in later testing,⁷³ necessitating product withdrawals or new warnings.⁷⁴⁻⁷⁶ Definition of uncertainties may suffer when much more safety and efficacy assessment is shifted to the postmarketing period, forcing prescribers to make decisions without complete information — especially if such information does not emerge for years, or ever,^{77,78} as can occur when a drug is approved through nonstandard criteria and then becomes difficult to study further in randomized clinical trials.

CONCLUSIONS

The FDA plays a crucial role in protecting the health of the public while approving new treatments in a timely fashion. Twenty-five years of experience with user fees has shown that, in the face of inadequate public funding of the personnel budget of the FDA, increased funding by its regulated industries can indeed improve regulatory timelines. This increased speed has also raised questions related to the decisions being made and the growing reliance of the agency on financial support from the companies it regulates, as the user-fee model has fundamentally changed the way that the FDA interacts with industry. In a different political climate, adequate public funding in place of user fees would allow the FDA to continue its current performance levels while adding further confidence that the public remains the primary client of the FDA.

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