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Perspective

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User Fees and Beyond — The FDA Safety and Innovation Act of 2012

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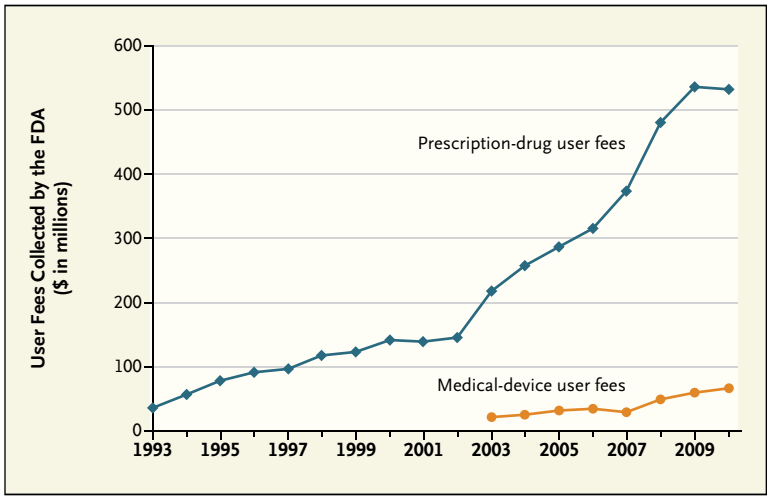
President Barack Obama recently signed into law the Food and Drug Administration (FDA) Safety and Innovation Act (FDASIA),[1] ending a long discussion among regulators, industry representatives, legislators, and patient advocates. The driving force behind the legislation was the need to reauthorize statutorily defined user fees that pharmaceutical manufacturers (since 1992) and medical-device manufacturers (since 2002) have paid when they submitted applications to the FDA for the evaluation of new products. The bill sailed through a closely divided Congress for two main reasons. First, most policymakers understand that because of chronic underfunding of the FDA by the federal government, these fees have become essential components of the agency's budget — particularly on the drug side, where they have amounted to more than $500 million annually in recent years (see graph). User fees have become required for the continued daily operation of the agency as it pursues its mission of protecting the public health. Second, the FDA and industry had reached agreement on important elements of the legislation and presented Congress with their plans to guide the law's development.

Apart from user fees, a major focus of FDASIA is streamlining the process of premarketing review of drugs and devices. For example, the legislation broadens the scope of the fast-track designation and the accelerated approval process for drugs for "serious or life-threatening" conditions. It requires the FDA to consider as clinical end points in the study of these drugs "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

The FDA is also given the authority to designate a new drug candidate as a "breakthrough therapy" if "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies [for serious or life-threatening conditions] on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development." When a drug is classified as a breakthrough therapy, the FDA will work closely with its



User Fees for Reviews of Prescription Drugs and Medical Devices Collected by the Food and Drug Administration (FDA) since 1993.

Prescription-drug user fees are collected by the Center for Drug Evaluation and Research, and medical-device user fees are collected by the Center for Devices and Radiological Health. Data are from the FDA (www.fda.gov).

manufacturer to expedite development and review — for example, "taking steps to ensure that the design of the clinical trials is as efficient as practicable." Although it is important to encourage the efficient development of transformative drugs, recent data show that the FDA already approves most products more quickly than other similar agencies[2] — including drugs for serious and life-threatening conditions.[3] But FDASIA opens up current expediting mechanisms to many more drugs, including those showing therapeutic promise on the basis of limited data, such as "pharmacologic" outcomes.

In the device market, industry representatives have frequently cited inefficiencies in the FDA's evaluation of applications as a barrier to bringing innovative products to market. On this point, the FDA website describes FDASIA as representing a "commitment between the U.S. medical device industry and the FDA" to improve the efficiency of regulatory processes and reduce time to market. Improved efficiency will be achieved in part by means of tighter performance targets for reviewing devices through each major regulatory pathway. For example, by 2016, the FDA must issue decisions within 90 days for 95% of devices following the 510(k) track used for most moderate-risk devices, which requires manufacturers to prove only that their device is substantially equivalent to a previously approved device. The law also directs the FDA to allocate user-fee revenue toward efforts such as reducing staff turnover, which industry sees as a barrier to efficient application review. FDASIA emphasizes additional premarketing interactions between sponsors and the FDA, including the creation of formal timelines for responding to manufacturers' presubmission inquiries. Despite calls from some stakeholders to rethink premarket approval and 510(k) substantial-equivalence device-evaluation systems, FDASIA does not change the general framework for bringing new devices to market or the standard of evidence required for doing so.

Other provisions cover the development of new drugs and devices in areas of particular need or novelty. For example, one section focuses on the development of new antibiotics, offering extensions of market-exclusivity periods for manufacturers and directing the FDA to reconsider its standards for preclinical studies of these products. Another section addresses the premarketing study of unapproved high-risk devices under investigational device exemptions (IDEs). Previously, the FDA would grant an IDE for a pivotal study only if the proposed study could potentially support eventual decisions regarding the marketing approval of the device in question. FDASIA removes this criterion and allows a sponsor to receive approval for an IDE study even if the FDA does not think the study will be sufficient to support a marketing application.

In recognition of the growing role of health information technology in health care, FDASIA also directs the FDA to derive, within 18 months, a strategic framework for information-technology regulation that "promotes innovation, protects patient safety, and avoids regulatory duplication." This framework is intended to include mobile medical applications, an area in which there is rapid growth and regulatory ambiguity, despite important potential risks to patients.

Enhancements to the postmarketing evaluation of drugs and devices received comparative-

ly less attention in FDASIA. Though many experts have called for substantial changes to the postmarketing surveillance of medical devices in particular, reforms specified in the legislation were generally limited to several areas of "program development" — requests for the FDA to develop frameworks, strategies, or processes related to improving postmarketing surveillance and enforcement. For example, the FDA was directed to create a program to evaluate device-recall data with the goal of minimizing the negative impact of recalls on public health; to include medical devices in the current Sentinel program for drugs, an early-stage program aimed at developing data sources and designing methods for identifying signals of safety concerns; and to propose a draft rule, which has now been released, for "unique device identifiers" as a mechanism for better tracking of device-related events.

In the realm of pharmaceutical products, FDASIA aims to help streamline the approval of generic drugs, as well as to ensure the safety of the drug supply and distribution chain. First, the law extends user fees to the manufacturers of generic drugs to provide greater funding for the FDA's generic-drug reviewers and thereby reduce the backlog of applications for the approval of such products. However, the law does not address the strategies that currently prevent approved generic drugs from reaching the market.[4] The legislation also contains provisions aimed at bringing attention to and assuring the safety of the drug supply chain, which has emerged as a growing concern. Currently, 80% of all active ingredients and 40% of drug tablets sold in the United States originate overseas. The FDA has traditionally had limited resources for inspecting non-U.S. facilities, so FDASIA provides directions for more frequent inspections and greater transparency regarding the origins of final products.

Although FDASIA ensures that the FDA will receive the ongoing user-fee funding it needs in the absence of realistic government appropriations and includes new initiatives that may help promote review efficiency, it missed an opportunity to promote more robust postmarketing systems to validate the effectiveness and ensure the safety of marketed products. For example, a greater proportion of user fees might have been directed toward personnel who serve surveillance functions such as analysis and aggregation of adverse-event reports, toward research evaluating novel ways of analyzing postmarketing data, or toward facilitating the development of infrastructure such as targeted registries. Additional provisions might have included more specific penalties for missing postapproval commitments or mechanisms for industry to share postmarketing data currently viewed as proprietary, with the goal of detecting important safety signals. Indeed, when the more efficient premarketing processes for drugs and devices envisioned by FDASIA are implemented, the number of drugs and devices requiring rigorous postapproval surveillance will only increase.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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France's New Framework for Regulating Off-Label Drug Use

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Off-label use of drugs is relatively common in medical practice, even if it's often not supported by strong scientific evidence. Studies in the United States have shown that off-label use may account for approximately 20% of prescriptions, or 150 million prescriptions per year.[1] In addition to its economic effect on the health care system, the inappropriate off-label use of drugs