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Reauthorizing the Prescription Drug User Fee Act: How are PDUFA, the FDA Budget, and Drug Safety Related?

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Reauthorizing the Prescription Drug User Fee Act

About this Paper

The Prescription Drug User Fee Act (PDUFA) authorizes the Food and Drug Administration to collect fees from brand-name drug manufacturers that are dedicated primarily to reviewing new drug applications for human use. The law, first enacted in 1992 and twice reauthorized, will expire Sept. 30, 2007, unless Congress acts.

Although FDA has met its primary PDUFA goal of speeding the review of new products, questions about the law's impact on drug safety and funding dominate current debate. To inform that debate as reauthorization is considered, this paper examines:

- ▶ Current law and FDA's proposed revisions, which would enable the agency to collect more revenue; enhance premarket review; and revise the postmarket safety system.
- ▶ The impact of PDUFA on the FDA's budget and on drug safety. The agency has shifted resources from research, training, field inspections and other activities in order to meet its commitment to timely drug reviews. Outside evaluations by the Institute of Medicine and others, coupled with several highly publicized safety problems, have raised questions about FDA's current approach to post-marketing surveillance.
- ▶ Proposals to enhance drug safety. These include financing the FDA through federal revenues rather than industry fees; strengthening information technology; and developing risk-monitoring strategies at the time of approval.

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About the Rapid Health Policy Response Project

The Rapid Health Policy Response Project of the School of Public Health and Health Services at The George Washington University presents data and other background information on breaking public health stories. The goal is to educate the public, policymakers, legislators, health care providers, the media and others in order to promote informed decisionmaking. Karyn Feiden, an independent consultant who writes about public health and health care, provides editorial support for this project. Financial support comes from the Public Health and Policy Group of Pfizer Inc.

Reauthorizing the Prescription Drug User Fee Act: How are PDUFA, the FDA Budget, and Drug Safety Related?

The Prescription Drug User Fee Act (PDUFA) authorizes the Food and Drug Administration (FDA) to collect fees from brand-name drug manufacturers that are dedicated primarily to the review of new drug applications for human use. The law, first enacted in 1992 to bring drugs to market more quickly, imposes specific performance goals on the FDA and has enabled the agency to virtually double its drug review staff and to upgrade its information technology systems substantially.¹

Evidence suggests that FDA has met its primary PDUFA goal of speeding the review of new products, primarily by increasing the size of the review staff. Median review time for standard new drugs was 27 months in 1993, 14 months in 2001 and 10.5 months in 2004.² Similarly, the median review time for priority drugs—those for serious and life-threatening diseases that lack satisfactory treatments—was 21 months in 1993 and six months in 2004. Dozens of cancer therapies have been reviewed and approved within three or four months, including Gleevec, for a rare form of leukemia, and Velcade, an injection to treat multiple myeloma. Therapies for AIDS and hepatitis C were also on the market less than four months after new drug applications were submitted to the FDA.³

Despite these successes, questions about the impact of PDUFA on drug safety dominate current debate.⁴

Reauthorizing PDUFA

PDUFA, which has twice been reauthorized with modifications by Congress (PDUFA II in 1997 and PDUFA III in 2002), is set to expire on Sept. 30, 2007, unless Congress acts. Current law:¹

- ▶ Sets as a goal that the FDA reviews and acts on 90 percent of the applications it receives for new drug and biological products within 10 months of their receipt (six months for priority therapies).
- ▶ Seeks to improve FDA interaction with industry by establishing timetables to guide FDA's meetings with drug sponsors, its dissemination of meeting minutes, and its responses to questions.
- ▶ Authorizes the FDA to spend user fees on certain drug safety activities for up to two years after a product has been approved (three years for products that require special risk management). This provision was included under PDUFA III, the first time the law was used to fund any postmarketing initiatives.

To increase public accountability, Congress also added a provision to PDUFA III requiring the FDA to undertake discussions with the regulated industry, scientific and

academic experts, and representatives of patient and consumer advocacy groups before recommending changes to the law. Following those discussions, the FDA published its recommendations for PDUFA IV in the *Federal Register* in January 2007;¹ after a period of public comment, the agency submitted slightly modified draft legislation to Congress,⁵ which is now under review.

The PDUFA IV proposal would:

- ▶ **Increase revenue targets** to allow the FDA to collect more money in user fees. For FY 2008, PDUFA IV sets a base target revenue of \$392.8 million, an \$87.4 million increase over PDUFA III.⁶
- ▶ **Enhance the premarket review** process by clarifying the nature of the data industry must submit to support its claims; establishing a schedule for discussing product labeling and postmarketing follow-up; and improving the information technology infrastructure.
- ▶ **Revise the postmarket drug safety system**, allowing PDUFA fees to be used for the first time for a broad-based overhaul, and lifting the time limit on PDUFA-funded safety assessments after a drug has been approved. An estimated \$29.3 million would be spent to enhance and modernize the current system.

In a related initiative, also described in the January, 2007 *Federal Register* document, the FDA has proposed a separate system of user fees to fund advisory reviews of industry's direct-to-consumer television advertising. In exchange for voluntarily seeking the FDA's pre-broadcast input, companies would get the agency's timely judgment on the accuracy and balance of their ads.

The Impact of PDUFA on the FDA Budget

In FY 2006, PDUFA funds accounted for 42.5 percent of FDA's total human drug program budget of \$521 million (and for more than half the funds dedicated specifically to drug review).⁷ The rest comes from appropriations allocated by Congress as part of the federal budget process.

Resource shortfalls have been a longstanding challenge to the FDA, as repeatedly noted by the many advisory committees established over the decades to strengthen the agency. In 1955 and again in 1962, for example, Citizen Advisory Committees on the FDA said the agency had insufficient funds, staff and facilities to meet the demands it faced. In May 1991, the Advisory Committee on the Food and Drug Administration noted that "the FDA's grave resource limitations impose sometimes staggering burdens on the Agency."⁸ And as recently as this year, the Institute of Medicine wrote, "an agency whose crucial mission is to protect and advance the public health should not have to go begging for resources to do its job."⁹

Many FDA scientists agree. In a survey by the Union of Concerned Scientists, nearly 70 percent of 1,000 respondents did not believe the FDA had sufficient resources to effectively perform its mission of "protecting the public health and... helping the public get

the accurate, science-based information they need to use medicines and foods to improve their health.”¹⁰

In order to collect and spend user fees, PDUFA requires the FDA to dedicate a certain level of appropriated federal dollars to the drug review process. Most of that pays for salaries, since more than 80 percent of the FDA’s total budget supports the agency’s workforce. To meet its commitment to timely drug reviews, the FDA has shifted staff away from other activities, especially research, training and field inspections, and kept staff positions, including those of medical officers and statisticians, vacant when they become open. The result has been a rather dramatic redistribution of personnel within the agency.¹¹

The Government Accountability Office has documented the following trends.¹²

- ▶ The percentage of the FDA’s total budget used to pay for reviewing drugs and biologics increased from 17 percent (\$120 million) in 1992 to 29 percent (\$314 million) in 2000.
- ▶ The percentage of full-time-equivalent staff engaged in reviewing drugs and biologics increased from 14 percent in 1992 to 26 percent in 2000. The number of FTEs engaged in product review grew from 1,277 to 2,346 while staff involved in other FDA activities fell from 7,736 to 6,571.

In a report issued in January 2007, the Institute of Medicine (IOM) noted that these resource shifts have altered the balance “between FDA’s dual goals of speeding access to innovative drugs and ensuring drug safety over the product’s lifecycle.”⁹

Concerns about the Drug Safety System

Not surprisingly, then, the issue of drug safety has taken center stage in discussions of PDUFA reauthorization. Because information about approved products evolves as those products are used by more people over a longer period of time, an effective postmarketing system for monitoring risks and benefits is essential. Several highly publicized problems—notably among the COX-2 inhibitors, (painkillers that include Vioxx and Celebrex), selective serotonin reuptake inhibitors (SSRIs, used to treat depression), and the antibiotic Ketek—have raised questions about FDA’s current ability to identify adverse effects after a drug is approved for sale to the public.

Responsibility for drug approvals, and for any necessary postmarketing regulatory action, currently rests with the Office of New Drugs (OND), the largest office within FDA’s Center for Drug Evaluation and Research (CDER). A separate CDER office, the Office of Surveillance and Epidemiology (formerly the Office of Drug Safety), serves primarily as a consultant to OND after drugs have been approved. Drug manufacturers are required to report serious and unexpected adverse events to FDA within 15 days of learning about them; health care providers and patients may file reports voluntarily. The FDA can mandate postmarketing studies only under specific and limited circumstances, most commonly when priority drugs have been approved on an accelerated basis.

The FDA's approach to drug safety has recently been examined by the:

- ▶ **Institute of Medicine**, which concluded that the drug safety system is impaired by “serious resource constraints that weaken the quality and quantity of the science that is brought to bear on drug safety; an organizational culture in CDER that is not optimally functional; and unclear and insufficient regulatory authorities, particularly with respect to enforcement.”⁹
- ▶ **Government Accountability Office**, which concluded that “FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues.... There is a lack of criteria for determining what safety actions to take and when to take them.”¹³

The Pharmaceutical Research and Manufacturers of America responded to the IOM report with a promise to review its recommendations. At the same time, it identified the real challenge as making “a good system better” and noted that “fewer than three percent of approved prescription drugs have been withdrawn from the American market for safety reasons over the past 20 years.”¹⁴

PDUFA and Drug Safety: Daniel Carpenter, PhD, professor of government at Harvard University, and colleagues looked specifically at the impact of PDUFA deadlines on the timing of drug approvals and the post-market experience of those drugs.¹⁵

Under current law, the “PDUFA clock” starts ticking as soon as a drug company submits a new drug application. Although the FDA has strong incentive to meet its review deadlines, performance measurements are unaffected if the agency ultimately hands down a decision one month or six months after a missed deadline. That framework may help to explain the two key findings in Carpenter’s analysis:

- ▶ The PDUFA clock has dramatically influenced FDA review behavior, such that a high proportion of approvals are concentrated in the months and weeks just before the deadline, and relatively few occur shortly afterwards.
- ▶ PDUFA deadlines appear to influence FDA decisions that may have an impact on drug safety. Based on an analysis of six measures, including frequency of labeling revisions and safety-based withdrawals from the market, the authors conclude, “the rate at which drugs experience post-marketing regulatory events is appreciably higher for drugs approved in the months before the PDUFA clock deadlines, compared to others.”

Enhancing Risk Management: A number of observers have emphasized the importance of improved information technology and urged industry to expand its own strategies for ensuring drug safety. For example:

- ▶ In testimony before the Senate Committee on Health, Education, Labor and Pensions, former FDA Commissioner Mark McClellan called for establishing a routine electronic system for conducting population-based, post-marketing monitoring. The heart of his proposal is a public-private surveillance network built on existing data sources, including private health insurers, Medicare and Medicaid.¹⁶

- ▶ A PricewaterhouseCoopers report called on the industry to build more integrated, flexible and proactive “pharmacovigilance programs”—defined as the systematic detection, assessment, understanding and prevention of adverse drug reactions—into existing research and development practices.¹⁷
- ▶ A panel of industry leaders convened by the Tufts Center for the Study of Drug Development called for the collection of higher quality safety data, and urged that evaluation be integrated more seamlessly throughout the drug development and commercialization process.¹⁸

Perspectives on PDUFA Reauthorization and New Legislation

The FDA has reported that most public comments responding to its proposed PDUFA recommendations favored reauthorization.⁶ Nonetheless, supporters of financing FDA activities via appropriations from general federal revenues, rather than from industry user fees, include:

- ▶ **Four former FDA Commissioners**, who spoke at a February 2007 policy workshop at The George Washington University.¹⁹ Frank Young, MD, PhD, commissioner from 1984 to 1989, said early proposals for user fee legislation reflected “a moment of desperation. No one really wanted to go this route. I would strongly say that the Congress has let the agency down with putting on requirements and not providing budget.”
At the workshop, Young asked his colleagues, “Given a choice of having PDUFA or an appropriation of equal amount, which would you take?” The other commissioners spoke with a single voice. “Appropriations,” said David A. Kessler, MD, JD, whose tenure from 1990 to 1997 coincided with the enactment of the first PDUFA law. “No question.”
- ▶ **Institute of Medicine report**, which stated, “Congressional appropriations from general tax revenue are a mechanism by which the public can directly, fairly and effectively invest in the FDA’s postmarket drug safety activities.”⁹
- ▶ **Consumer groups**, which issued statements as part of a public meeting held Feb. 16, 2007 to gather stakeholder views on PDUFA IV recommendations. The Consumers Union, the National Research Center for Women and Families and the Center for Medical Consumers all expressed a preference for full FDA funding through federal appropriations.²⁰
- ▶ **Twenty-two experts in drug safety and regulatory issues**, who signed an open letter to Congress calling for full FDA funding through appropriations and a reauthorization of PDUFA only long enough to reform the current system. Signatories included three former editors-in-chief of the *New England Journal of Medicine*, four members of the IOM drug safety committee, and six former senior HHS and FDA officials.²¹

A Pharmaceutical Research and Manufacturers of America spokesperson has said the industry would be happy to have Congress fully fund the FDA, but did not expect it to happen.²²

Critics of the proposed PDUFA reauthorization have suggested that patients and consumers were only minimally consulted as FDA developed its recommendations and that safety-related provisions are inadequately funded, vague, and lacking measurable standards. Some also argue for mandatory pre-clearance of direct-to-consumer advertisements and for the lifting of all restrictions on how the agency can spend PDUFA funds for postmarket activities.^{23, 24}

Industry trade associations, however, generally support the PDUFA reauthorization provisions:

- ▶ **The Pharmaceutical Research and Manufacturers of America** applauds PDUFA IV for making funds available “for improving drug development, drug safety and the information technology system,” including resources for “additional safety officers, new information management systems, and improved access to drug safety data bases.”²⁵
- ▶ **The Biotechnology Industry Organization** (BIO) says that PDUFA provides “FDA the resources it needs to continue to make sound scientific, medical and regulatory decisions.” BIO also says that proposed enhancements would allow FDA “to modernize the post-market surveillance system, evaluate more efficiently each product’s unique benefits and risks, and continue to support the timely development and availability of new medicines to patients.”²⁶

Guided in part by recommendations contained in the IOM and GAO reports, several bipartisan bills recently introduced in the 110th Congress include a focus on drug safety:

- ▶ “Enhancing Drug Safety and Innovation Act of 2007” (S 484), sponsored by Senators Edward Kennedy (D–MA) and Michael Enzi (R–WY), would require the FDA and the drug companies to develop a plan for monitoring risk at the time a product is approved.²⁷
- ▶ “Food and Drug Administration Safety Act of 2007” (S 468), sponsored by Senators Chris Dodd (D–CT) and Charles Grassley (R–IA), would create a Center for Post Market Drug Evaluation & Research that reports directly to the FDA Commissioner.²⁸

Similar legislation has been introduced into the House.²⁹

Other FDA-related legislation under consideration focuses on transparency, public access to clinical trial data, and the role of advisory committees.³⁰ Whether any of this legislation is ultimately linked with the PDUFA legislation, or considered separately, the current debate reflects a widespread recognition that even at its best, “FDA approval does not represent a lifetime guarantee of safety and efficacy,” as IOM reports.⁹

However, transforming the drug safety system through “a lifecycle approach to drug risk and benefit,” the approach IOM recommends, would change how FDA does business in some very fundamental ways. Identifying and implementing sound strategies for making those changes is a crucial public health goal.

Notes and Sources

- ▶ 1. [The Federal Register 72:9 1743-53](#), Jan. 16, 2007, describes the evolution and current provisions of PDUFA. [Prescription Drug User Fees](#) on the FDA web site provides links to performance and financial reports and other background materials.
- ▶ 2. Data on 1993 and 2001 drug approval times are noted in U.S. Government Accountability Office, “[Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawal and Other Agency Activities](#).” Washington, DC: September 2002. For 2004 and preliminary 2005 data, see Food and Drug Administration, “[Performance Report to the President and Congress for the Prescription Drug User Fee Act](#),” FY 2005.
- ▶ 3. Rados C, “[The FDA Speeds Medical Treatments for Serious Diseases](#).” FDA Consumer, March–April 2006.
- ▶ 4. The Web site of the Project on Scientific Knowledge and Public Policy (SKAPP) at The George Washington University’s School of Public Health and Health Services provides links to most major background documents relating the reauthorization of PDUFA and drug safety. See “[The Impact of Prescription Drug User Fees on Drug Safety – Reports and Analyses](#).” SKAPP engages scholars and scientists in examining how scientific evidence is applied in legal and regulatory arenas.
- ▶ 5. “Prescription Drug User Fee Amendments of 2007.” Proposed draft legislation and section-by-section summary submitted to Speaker of the House Nancy Pelosi, March 16, 2007, by the Secretary of the Department of Health and Human Services.
- ▶ 6. FDA press release, “[Final PDUFA Recommendations Transmitted to Congress Will Strengthen Drug Review and Drug Safety](#).” March 23, 2007.
- ▶ 7. The FDA Alliance, “[Education and Advocacy to Increase the Appropriate Resources Available to FDA](#).” Presentation to the Congressional Research Service, Dec. 18, 2006.
- ▶ 8. Advisory Committee on the Food and Drug Administration, Final Report, May 1991. This source also provides the historical notes about the 1955 and 1962 Citizen Advisory Committees.
- ▶ 9. Committee on the Assessment of the US Drug Safety System, Institute of Medicine, [The Future of Drug Safety: Promoting and Protecting the Health of the Public](#). Washington, DC: National Academy of Sciences, 2007.
- ▶ 10. Union of Concerned Scientists, “[Summary of the FDA Scientists Survey](#),”

2007. See also, Union of Concerned Scientists, "[Voice of Scientists at FDA: Protecting Public Health Depends on Independent Science](#)," 2006. The surveyed respondents were FDA employees "who had scientific job titles (such as biologist or chemist), scientific duties (such as consumer safety officer or medical officer), or scientific qualifications necessary for their jobs (such as project management officer)."

- ▶ 11. Feigal DW, "[Impact of Resources](#)." Presented at "Policy Workshop on Strengthening the FDA," Project on Scientific Knowledge and Public Policy, GW's School of Public Health and Health Services, Washington, DC: Feb. 22, 2007 (invitation-only session).
- ▶ 12. U.S. Government Accountability Office, "[Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawal and Other Agency Activities](#)." Washington, DC: September 2002.
- ▶ 13. U.S. Government Accountability Office, "[Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process](#)." Washington, DC: March 2006.
- ▶ 14. Press release, "[PhRMA Statement on the IOM Drug Safety Report](#)." Sept. 22, 2006.
- ▶ 15. Carpenter D., et al., "[Deadline Effects in Regulatory Drug Review: A Methodological and Empirical Analysis](#)." March 2007. Unpublished. Presented at "Policy Workshop on Strengthening the FDA," Project on Scientific Knowledge and Public Policy, GW's School of Public Health and Health Services, Washington, DC: Feb. 22, 2007 (invitation-only session).
- ▶ 16. McClellan M., "[Fundamental Improvements in Drug Safety for the 21st Century: Time for a Systematic, Electronic Infrastructure](#)." Testimony before Senate Committee on Health, Education, Labor and Pensions, March 14, 2007.
- ▶ 17. Pricewaterhouse Coopers, "[Unlocking the Power of Pharmacovigilance: An Adaptive Approach to an Evolving Drug Safety Environment](#)," 2007.
- ▶ 18. Tufts Center for the Study of Drug Development, "[New Approaches to Assessing Drug Safety Will Help Reduce Development Time and Costs](#)." April 24, 2006.
- ▶ 19. The FDA commissioners made their comments at "Policy Workshop on Strengthening the FDA," Project on Scientific Knowledge and Public Policy (SKAPP), GW's School of Public Health and Health Services, Washington, DC: Feb. 21, 2007 (public session). These remarks are available through www.kaisernetwork.org in [transcript and webcast formats](#).

- ▶ 20. Among the statements made at the FDA's public meeting on PDUFA, Feb. 16, 2007: [Consumers Union](#); the [National Research Center for Women and Families](#); and the Center for Medical Consumers.
- ▶ 21. [Open letter](#) to Senators Edward Kennedy and Mike Enzi, and Representatives John Dingell and Joe Barton, March 14, 2007.
- ▶ 22. Skrzycki C, "[FDA 'Addiction' to User Fees Comes Under Attack](#)," Bloomberg News, April 4, 2007.
- ▶ 23. [Consumers Union](#) and the [National Research Center for Women and Families](#) prepared statements for the FDA's public meeting on PDUFA, Feb. 16, 2007 about consumer input, drug safety, and direct-to-consumer advertising. See also Avorn J, "[Merck's Multibillion-Dollar Bet](#)," Boston Globe, Feb. 18, 2007 and Angell M, "[Taking Back the FDA](#)," Boston Globe, Feb. 26, 2007.
- ▶ 24. See, for example: Institute of Medicine's [The Future of Drug Safety](#), p. 13, "Congress should greatly reduce current restrictions on how CDER uses PDUFA funds" and [National Research Center for Women and Families](#), Feb. 16, 2007 statement, "It is essential that industry funding does not influence approval decisions or other regulatory decisions."
- ▶ 25. PhRMA statement on PDUFA Reauthorization Proposals. [Press release](#). Washington, DC: Jan. 11, 2007.
- ▶ 26. Biotechnology Industry Organization. Statement at the FDA's public meeting on PDUFA, Feb. 16, 2007.
- ▶ 27. [Enhancing Drug Safety and Innovation Act of 2007](#) (S 484).
- ▶ 28. [Food and Drug Administration Safety Act of 2007](#) (S 468).
- ▶ 29. [Enhancing Drug Safety and Innovation Act of 2007](#) (HR 1561), sponsored by Representatives Edward J. Markey (D-MA) and Henry Waxman (D-CA). [Food and Drug Administration Safety Act of 2007](#) (HR 788), sponsored by Reps. John Tierney (D-MA) and Jim Ramsted (R-MN).
- ▶ 30. Other legislation under consideration in the 110th Congress includes [Fair Access to Clinical Trials](#) (S. 467), sponsored by Senators Chris Dodd (D-CT) and Charles Grassley (R-IA) and [Swift Approval, Full Evaluation \(SAFE\) Drug Act](#) (HR 1165), sponsored by Representative Edward J. Markey (D-MA). The Food and Drug Administration Improvement Act of 2005 (HR 2090) was introduced in the 109th Congress, but has not yet been reintroduced.