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The Prescription Drug User Fee Act: Structure and Reauthorization Issues

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Summary

In 1992, Congress passed The Prescription Drug User Fee Act (PDUFA) to speed up the approval of pharmaceuticals in the United States. The legislation created sections 735 and 736 of the Federal Food, Drug and Cosmetic Act (FFDCA), authorizing the Food and Drug Administration (FDA) to collect user fees from drug manufacturers in exchange for the faster review of drug and biological products. The law stipulated that the additional user fee revenues could only be used for activities necessary to the review of human drug applications. It also specified that the revenues raised under the program had to be "in addition to" baseline monies already dedicated to drug approvals. As Congress decides the agency's annual appropriation each year, it sets out the total amount of user fees that can be assessed during the upcoming fiscal year. To go with the user fee authority, but separate from the law, the FDA, drug and biotech industries settled on specific annual performance goals that were laid out in letters of agreement between the agency and Congress. To meet these goals, FDA hired nearly 600 new reviewers, and upgraded its information system for tracking pending drug applications. Congress authorized the first user fee program, referred to as PDUFA I, to run for a period of 5 years.

The original user fee law was reauthorized by Congress as part of the 1997 Food and Drug Administration Modernization Act (FDAMA). Under the reauthorized statute, known as PDUFA II, agency and industry representatives agreed to a new set of annual performance goals to encourage the timely processing of marketing applications. The FDA continued to hire more drug reviewers under PDUFA II, so that today, more than 1,000 employees' salaries are supported by user fee revenues. The funding for PDUFA II would have expired on September 30, 2002.

The FDA and the pharmaceutical industry generally agree that the user fee program has, to a large extent, been fairly successful. However, the program does have its critics who argue that the quicker review process could be compromising drug safety. To them, the number of prescription drugs withdrawn in recent years is evidence that speedier approvals may be jeopardizing the health of some patients.

The 107th Congress reauthorized drug user fees in June 2002 as part of the bioterrorism bill (P.L. 107-188). Known as PDUFA III, the legislation extended the law for 5 more years, authorized various post-marketing activities to ensure the monitoring of drug safety, and allowed the agency to use user fees to review adverse event reports for drugs approved after October 1, 2002. The new law requires FDA to announce on its Internet site when drug manufacturers fail to complete 'Phase IV' post-market studies. In these situations, the agency may require companies to notify health practitioners who prescribe the drug of that failure and of the questions of clinical benefit, and, where appropriate, the questions of safety that remain unanswered as a result. In addition, the Act authorized funding increases for three FDA offices: the office of drug safety; the division of drug marketing, advertising and communications; and the office of generic drugs. This report will be updated as events warrant.

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Introduction

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA).[1] The law amended the Federal Food, Drug, and Cosmetic Act (FFDCA), authorizing the Food and Drug Administration (FDA) to collect from pharmaceutical companies user fees that would be used to speed up the review and approval of drugs and biologics.[2] At the time, Congress was growing increasingly concerned about the sizeable backlog of drug applications waiting for the FDA's review and the effect the delay could be having on patients who could benefit from the new therapies. Up until the user fee agreement, the review of applications for new drug products was, like most other government services, paid for with general revenues from the U.S. treasury. With PDUFA, Congress intended that the user fees would provide funds to help cover the cost of reviewing marketing applications for pharmaceutical products.

Under the terms of the 1992 Act, which is often referred to today as PDUFA I, funds from user fee collections could only be used for specified activities – primarily to hire additional reviewers to conduct faster reviews and reduce the backlog of pending new drug applications. As directed by the legislation, FDA with the drug industry prepared a detailed set of performance goals, separate from the Act, that were to be met each year in reviewing new drug marketing applications. Its plan for meeting these goals was spelled out in letters to the chairmen of the agency's authorizing committees. (Congress had no say in preparing these goals but has used its oversight authority to follow the agency's progress toward meeting them.) In the program's first several years, most of the money generated by user fees was spent on hiring additional reviewers, and upgrading the agency's computer information system for tracking the status of drug applications.

Encouraged by the success of the user fee program, Congress reauthorized the Act in 1997 as a major provision of the Food and Drug Administration Modernization Act (FDAMA).[3] With this new authorization, Congress mandated tighter performance goals, more transparency in the drug review process, and better

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[1] P.L. 102-571. 21 U.S.C. §379(g); 106 Stat. 4494; known as PDUFA I.

[2] The term "biologics" refers to vaccines, *in vivo* diagnostic allergenic products, and products made from intact cells or microorganisms like viruses, bacteria, fungi, etc.

[3] P.L. 105-115. Title 1, Sections 103(a) to (g); 111 Stat. 2299. See CRS Report 98-263 STM, *Food and Drug Administration Modernization Act of 1997 The Provisions*, by Richard Rowberg, B. Randall, Donna Porter, Bernice Reyes-Akinbileje, Donna Vogt and Diane Duffy.

communication with drug makers and patient advocacy groups. The reauthorized statute – known as PDUFA II -- expires on September 30, 2002.

FDA and the pharmaceutical industry feel that the user fee program has been successful but the program has its share of critics. They argue that speeding up drug application review has come at the expense of safety. They also argue that drug recalls, soon after approval, show the potentially hazardous consequences of faster approvals.

On June 12, 2002, President Bush signed P.L. 107-188, the Public Health Security and bio terrorism Preparedness and Response Act of 2002. In a section of this law, Title V, Subtitle A – Prescription Drug User Fees, the Prescription Drug User Fee Act was reauthorized and is known as PDUFA III.

The U.S. Drug Approval Process

Under the FFDCA, all drugs and biologics must be proven safe and effective before they can be approved by the FDA for marketing. As a first step in this process, a drug manufacturer, once it has come up with a drug candidate, conducts pre-clinical (i.e., animal) tests to determine whether the new chemical compound is safe enough to undergo further testing in human subjects. If animal tests confirm that the drug is indeed safe enough to be administered to patients, the drug company or sponsor will decide (almost always after consulting with the FDA) whether to file an investigational new drug (IND) application. An IND must contain detailed information about how the sponsor intends to test humans in clinical trials. By filing an IND, the sponsor seeks FDA's permission to conduct these studies.

In general, human studies, or clinical trials, are traditionally carried out in three phases, keeping with the testing protocol laid out in the IND application. In Phase I trials, the experimental drug is evaluated for safety in a small group of individuals who generally are healthy. In Phase II trials, the compound is given to a larger group of patients in a well-controlled clinical setting[4] to determine the dose needed to elicit the desired pharmacological effect. Since a drug's safety is always of paramount importance, investigators monitor for unwanted side-effects throughout all phases of testing. And finally, during Phase III studies, the new drug is given to an even larger group of patients, also in a well-controlled clinical setting, to further test whether the drug is effective in patients. If the results of the clinical studies indicate that the drug is safe and effective for its intended therapeutic uses(s), the manufacturer submits a new drug application (NDA) to FDA for its review and approval.

The clinical development and approval (i.e., licensing) of vaccines and biological products is quite similar to other pharmaceuticals. Vaccines and biologics manufacturers have to file INDs before they can conduct human studies, and similar to other drugs, clinical trials for biological products are usually carried out in three phases. If the clinical studies show that the vaccine or biologic is safe and effective,

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[4] In a typical comparative clinical trial, one group is given the drug under investigation and another, similar group is given an inactive compound (placebo), and the results are compared.

the sponsor submits a biologics license application (BLA) seeking agency review. All BLAs filed with the agency must be accompanied by a user fee. In this report, where user fees are mentioned with regard to drug applications, the reference can apply to the review of either NDAs or BLAs.

The typical NDA includes not only all of the raw statistical data about the drug's safety and efficacy, but also technical information about its basic chemistry and pharmacology, and information about how and where the finished product will be manufactured. Not until the NDA has undergone an evaluation, however, and the FDA is satisfied that the new drug is safe and effective for its intended medical use, will marketing approval be granted.[5]

The Prescription Drug User Fee Act: Its Implementation

Under PDUFA, the FDA is authorized to collect three categories of fees: a fee to cover the review for each drug or biologic application, i.e., NDAs and supplements;[6] an annual fee for each manufacturing establishment; and an annual fee for each product a drug company produces. A manufacturing establishment is defined as the place where at least one prescription drug is produced. A product fee is also charged for every prescription drug a company sells. Drug companies are required to pay the entire application fee when it or a supplement to an application is first submitted for FDA review. The establishment and product fees are paid on an annual basis.

Sections 735 and 736 of the FFDCA[7] authorize the FDA to set the fees each fiscal year so that the fee revenue from annual product and establishment fees will equal two-thirds of the total revenue received from the user fees, and the remaining one-third will come from the amount FDA expects to collect from drug application fees.[8] (See **Table 1.**) Note that the fee for a supplement to an application is one-half of the fee for a traditional NDA.

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[5] For more detailed information on the drug approval process, see CRS Report RL30989, *The U.S. Drug Approval Process: A Primer*, by Blanchard Randall IV; and CRS Report RL30913, *Pharmaceutical Research and Development: A Description and Analysis of the Process*, by Richard E. Rowberg.

[6] The term "supplement" here refers to an application submitted to FDA for the approval of a change to an already approved drug application.

[7] 21 U.S.C. Section 379(g) and (h).

[8] The rationale behind the inclusion of establishment and product fees was that application fees are not predictable, since the numbers of applications vary annually and sponsors cannot know with certainty the dates on which the application would be submitted to the agency. Therefore, the establishment and product fees were established to provide the FDA with a steady and predictable source of revenue, essential to keeping the program going. Holcombe, Kay. *PDUFA – a Primer*, unpublished paper, summer 1997.

The amount of the user fee to be charged for the review of a typical NDA in the upcoming year is based on FDA's estimate of the number and type of applications the agency estimates will be submitted in that next year. Such estimates are based primarily on historical records of how many applications were submitted in previous years. The agency also uses estimates of how many of the new applications will contain extensive clinical data and how much time it expects to spend on their review.

The total amount of revenue that can be collected from the various user fee categories combined is capped each year by Congress in FDA's annual appropriations act. Prior to requesting this total cap for the upcoming fiscal year, the agency calculates the fees and total fee revenues and adjusts these for inflation using either the average urban Consumer Price Index or the civil service base pay for federal employees in the District of Columbia, whichever is greater. Each year's inflation adjustment is added on a compounded basis to the sum of all the adjustments made for prior years. In summary, the total revenue from user fees collected after adjustments are made consists of one third from applications, one third from manufacturing establishments, and one third from product fees.

Table 1. PDUFA User Fee Charges FY1998--FY2002

	Fee rates				
Fee category	FY1998	FY1999	FY2000	FY2001	FY2002
Application fee for NDA/BLA with clinical trial data	$256,846	$272,282	$285,740	$309,647	$313,329
Supplemental application fee for NDA/BLA	$128,423	$136,141	$142,870	$154,823	$156,660
Establishment fee	$141,966	$128,435	$141,971	$145,989	$140,109
Product fee	$18,591	$18,364	$19,959	$21,892	$21,630

Source: [http://www.fda.gov/oc/oms/ofm/userfees/userfees.htm].

By law, the amount of each type of user fee charged can be reduced, or the fee can be waived for various reasons. For example, applications for drugs to treat rare diseases (so-called orphan drugs), and applications for generic drugs and over-the-counter drugs (not associated with a new drug) are exempt from user fees.[9] In addition, user fees can be reduced or waived to protect public health. They can also be waived if the fees would be a financial barrier to pharmaceutical innovation, or if they would exceed FDA's anticipated costs for reviewing the drug application. Brand-name drug makers can seek waivers if a fee would put them at an economic disadvantage relative to the producers of generic drugs, who, as mentioned above, are not required to pay user fees. Smaller pharmaceutical companies are not charged

[9] Other exemptions include large volume parenterals (injectable drugs) approved before September 1992; allergenic extract products, whole blood or a blood component for transfusion, in vitro diagnostic biologic products, and certain drugs derived from bovine blood. (See footnote 31.)

a user fee when they submit their first human drug application for agency review.[10] Until recently, exemptions were also given when drug companies filed supplements with the FDA to request a new use for a pediatric drug that was already approved for other uses. However, the user fee exemption for pediatric supplements was repealed in 2001 when Congress passed the Best Pharmaceuticals for Children Act.[11] After January 2002, drug companies submitting applications for new pediatric indications are charged user fees.

Table 2 shows the total number of dollars authorized and appropriated under PDUFA II. Each year, Congress authorizes how much can be collected from user fees in its annual appropriations bill for the FDA.

Table 2. PDUFA Funds: Authorizations and Appropriations of User Fees, FY1998-FY2002

($ in thousands)

Fiscal years	Total authorized collections in the FDA Modernization Act of 1997	Total user fee collections specified in annual appropriations acts[a]
1998	$106,800	$117,121
1999	$109,200	$132,273
2000	$109,200	$145,434
2001	$114,000	$149,273
2002	$110,100	$161,716

Source: FDA's Office of Financial Management.

[a] Under PDUFA I, user fees were not paid until FDA completed the final action on the drug application. This meant that a substantial part of fee revenue came into the agency in years subsequent to the application. These fee revenues, however, counted against the appropriation limit that applies to the fiscal year in which the application was initially submitted. The appropriation limit was adjusted each year for inflation. In general, these funds are available until they are spent. [21 U.S.C. §379(h)(g)(4)]. U.S. Department of Health and Human Services, Food and Drug Administration. Office of Financial Management, *Justification of Estimates for Appropriation Committees*. Fiscal Year 2003.

Restrictions in the Act

When PDUFA I was enacted a decade ago, the pharmaceutical industry and Congress wanted to make sure that additional user fee revenues would be used to speed up the review and approval of drug applications. With this goal in mind, they placed in the Act two statutory conditions or "triggers" that had to be met before any fees could be collected. As reauthorized under PDUFA II, the first "trigger," in

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[10] 21 U.S.C. 379h (d)(1). See also: U.S. Department of Health and Human Services. Federal Drug Administration. Office of Financial Management. Guidance For Industry, Fees-Exceed-the-Cost Waivers Under the Prescription Drug User Fee Act, June 1999. [http://www.fda.gov/cder/guidance/index.htm]

[11] P.L. 107-109. The Best Pharmaceuticals For Children Act, Section 5.

Section 736(f)(1) of the FFDCA, requires that user fees be assessed only if the agency's total annual appropriations – excluding user fees – for salaries and expenses for a given year are equal to or greater than its total appropriations for FY 1997, multiplied by whichever inflation adjustment factor (described above) is applicable for the fiscal year in question. In other words, PDUFA fees could not be a "substitute" for the agency's annual appropriation from general revenues.

The second "trigger," in Section 736(g)(2)(A) of the FFDCA, relates to how much FDA spends on activities connected to the review of human drug applications. The Act stipulates that the total user fees collected will equal the amount set in the appropriations act and requires that, at a minimum, FDA spend from its annual allocation of appropriated funds an amount equal to what the agency spent on these review activities in FY1997, as adjusted for inflation. It was the intent of Congress that PDUFA fees would be used to accelerate the drug application review process and not substitute for "normal level" expenses. PDUFA funds that are not spent before the end of the fiscal year remain available to the agency for the review of drug applications in subsequent years.[12]

Performance Goals

Under PDUFA I, the pharmaceutical and biologics industries and FDA agreed that the collected fees needed to be used exclusively to speed the review of NDAs and BLAs and to meet performance goals that set time limits under which the agency would review NDAs. The performance goals, formulated by the agency and the drug and biologics industries (Congress was not involved) were not included in the law; instead they were contained in letters sent after the law was enacted to the chairs of the House Energy and Commerce Committee and the Senate Labor and Human Resources Committee in 1992 (now the Committee on Health, Education, Labor, and Pensions) by the Secretary of Health and Human Services (HHS). The agency's success in meeting these goals was to be reported in two annual reports to Congress. The first concerned FDA's progress toward achieving the goals stated in the letters. The second, the financial report (called a "Fiscal Report"), explained how FDA implemented the user fee collection authority. These "report cards" were also delivered to the chairmen of the congressional committees named above.

When it came time to reauthorize PDUFA in 1997, Congress again did not include the performance goals in the statute. Instead, in FDAMA "Section 101. Findings," Congress stated that the fees were to be used to expedite the drug development and application review process as laid out in performance goals identified in letters sent by the Secretary of HHS to the chairman of the two authorizing committees in 1997 after the law was enacted. It also ordered the goals to be published in the *Congressional Record*. In addition, FDAMA "Section 104. Annual Reports" recognized the existence of these goals and required DHHS to send the two annual "report cards," mentioned above, to Congress. The requirement for these reports was not made part of the FFDCA.

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[12] U.S. Department Health Human Services. Food and Drug Administration. Final Financial Report of the Prescription Drug User Fee Act of 1992; FY1997 Report to Congress, February 1, 1998. [http://www.fda.gov/oc/pdufa/reports.html]

The most recent performance goals for the PDUFA III program are now referred to as "side agreements" by some. They also are not in the main text of the Act, but rather are referred to in the "Findings" section of Title V of P.L. 107-188. The actual performance goals were again agreed too only by the agency and the pharmaceutical and biologics industry representatives with no congressional involvement. They were set forth in letters from the Secretary of HHS to the chairman of the House Committee on Energy and Commerce and the chairman of the Senate Committee on Health, Education, Labor and Pensions. These "side agreements" will have no force of law. Rather, the goals as set out in the *Congressional Record* are recognized as policy for which FDA holds itself accountable. Congress, therefore, will use these goals as a starting point for oversight of the drug approval process.

PDUFA II Performance Goals. The goals for the last user fee program (under PDUFA II) were laid out in a November 12, 1997-letter from former Secretary of HHS, Donna Shalala, to Senator James M. Jeffords, then Chairman of the Senate Labor and Human Resources Committee. They reduced the amount of time that FDA had to review approval applications for the following categories: original new drug or biologic[13] applications (both priority and standard),[14] including new molecular entities (NMEs);[15] efficacy and manufacturing supplements;[16] and NDAs re-submitted with new clinical data. To meet these goals, the FDA, by the end of 2002, will have taken action on (i.e., either approve or disapprove) within 10 months of their submission date, 90% of all standard NDAs, biologic product license applications (BLAs), and effectiveness supplements. In addition, within 6 months of their submission date, the agency will have taken action on 90% of priority NDAs and BLAs. Furthermore, by the end of FY2002, the FDA will have reviewed 90% of all manufacturing supplements to NDAs and BLAs, and, within 4 months of submission, complete review of all supplements requiring the agency's prior approval. For manufacturing supplements that concern minor changes (e.g., different supplier of an inactive ingredient), the agency has completed its review within 6 months of submission.[17]

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[13] See footnote 2. The term "biologics" refers to vaccines, *in vivo* diagnostic allergenic products, and products made from intact cells or microorganisms like viruses, bacteria, fungi, etc.

[14] Applications for new drugs are typically assigned to one of two ratings for review: either "priority" or "standard." The designation is based on whether the new drug offers significant therapeutic advantages over existing therapies.

[15] New molecular entity (NME) refers to a new, chemically unique compound that is different from other drugs already on the market. NMEs usually take more time to review since there are no similar compounds to which they can be compared. NMEs also contain active substances that has never been approved for marketing in any form in the United States.

[16] Efficacy supplements amend already approved drug applications with new data on the effectiveness of the drug.

[17] U.S. Department of Health and Human Services. Food and Drug Administration. FY2000 PDUFA Performance Report to Congress for the Prescription Drug User Fee Act of 1992 as Reauthorized and Amended by the Food and Drug Administration Modernization Act of 1997, January 2001, p. 3. (Hereafter cited as HHS, FDA. FY2000 PDUFA Performance

(continued...)

Performance goals for the PDUFA II program included activities related to the investigational phases of a new drug's development. For example, as a goal under the reauthorized program, FDA agreed to:

- respond within 30 days after the sponsor submits new data after a clinical hold[18] has been placed on a product;
- respond to sponsors' appeals of a dispute resolution decision within 30 days after the agency receives the appeal; and
- respond to a request for an evaluation of a clinical trial protocol within 45 days of the agency receiving the request.[19]

The performance goals also required FDA to meet new management goals, particularly to hold more meetings with drug manufacturers during the IND testing phases of a new product's development. The performance goals also included specified time frames for meeting with, and responding to, drug sponsors' requests. For example, the agency must, within 30 days, prepare the minutes of all meetings with drug company personnel – outlining agreements, disagreements, issues for further discussion, and action items. As before, the law requires FDA to file two annual reports with Congress: an annual performance report within 60 days of the end of the fiscal year; and an annual financial report within 120 days of the end of the fiscal year. It is these reports that contain the "report card" on how well the agency complied with the performance goals set by itself and industry.

Performance Goals Under PDUFA III. On March 13, 2002, the Bush Administration released its performance goals for the PDUFA III program. The goals, worked out during private meetings between FDA officials and representatives of the U.S. pharmaceutical and the biotechnology industries, are not significantly different from those agreed to under PDUFA II nor did they have any congressional input. These goals are in letters to the chairmen of the authorizing committees after enactment of the reauthorized PDUFA.[20] The 2002 target for completion times of application reviews would remain the same, with a minor change – by 2007, the review period for resubmitted efficacy supplements would become 2 months compared to 6 months under PDUFA II performance goals.

The PDUFA III performance goals, however, contain several provisions that were not included in either PDUFA I or II performance goals.[21] One new proposal would let biotechnology companies, during the early development phase of a biotechnology product, request that FDA select an independent consultant (paid for by the sponsor) to participate in the agency's review of the protocols for the product's

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[17] (...continued)
Report.)

[18] A clinical hold is an order issued by FDA to an applicant to either halt, delay, or suspend an ongoing clinical trial.

[19] HHS. FDA. FY2000 PDUFA Performance Report.

[20] "Performance Goals for the Prescription Drug User Fee Amendments of 2002," *Congressional Record*, v.148, n.73, June 6, 2002, p. S5195.

[21] [http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html]

clinical studies. The basis for this proposal is that many new biological products are on the cutting edge of science, and FDA may not have the expertise to review the application in a timely way. Companies could ask for the outside consultant only if the biotechnology product submitted for approval offered a significant advance in the treatment, diagnosis, or prevention of a disease or condition, or met some other need. Requests for an outside consultant could come only if the sponsor had never submitted an application for that product before. If the request was granted, then a 60-day extension for scheduling meetings with FDA officials would be given. In FY2006, FDA will evaluate the costs and benefits of this proposal.

The agreement on goals also included two pilot programs to test the concept of a continuous, or "rolling," new drug application (NDA). According to the FDA, the purpose of the continuous review of applications is to reduce the amount of time it takes to develop and review "fast track products." Both pilots apply to products characterized in Section 506(a) of the FFDCA as "fast track products," or products for the treatment of serious or life-threatening conditions. Under the pilot programs, the FDA would review defined units or parts of the NDA as the manufacturer finishes them rather than waiting until the entire application is submitted. The first pilot will look at whether the evaluation of an application in smaller units – along with the additional feedback and advice that companies will gain during the development phase – will actually lead to quicker development and shorter review times.

For drugs and biologics that qualify for the first pilot, the agency will enter into an agreement with the sponsor to accept pre-submission of one or more "reviewable units" of the application in advance of the submission of the completed drug application. In the second pilot, the agency will reach an agreement with the drug sponsor to begin a formal program of frequent scientific feedback and interactions regarding the drug's development. The FDA will have to issue guidelines before September 30, 2003, describing how it will implement the pilot tests. Also, in FY2004 the agency will have to contract with outside consultants to evaluate whether the pilot programs have been effective.

The new goals also include, for the first time, an agreement that would allow FDA to use user fee money to support post-marketing surveillance activities. Under the proposal, over the next 5 years the agency would double, to almost 100, the number of staff assigned to monitor the side effects of drugs already on the market. To aid this heightened surveillance, the agency would encourage drug companies to include "risk management plans" in their pre-NDA/BLA meetings before discussions were held with agency officials about possible safety related issues that may arise later. As part of these discussions, which would usually take place between 6 and 12 months prior to the sponsor submitting an NDA, companies will be allowed to submit summaries of relevant safety information and their risk management plans for agency review. For drug and biologic applications or supplements that include clinical data, submitted on or after October 1, 2002, FDA will be able to spend some of the PDUFA fees to cover the additional cost of reviewing the risk management plans. Under the new goals, FDA can also use the fees to pay for the development of databases documenting the use of a commercial drug for the first 3 years post-approval if the agency has safety concerns. In addition, user fees can be used for "risk management" oversight for up to 2 years post-approval for most products, and

for up to 3 years in situations where the product's labeling included specific warnings. The agency refers to the time it would be monitoring the risk management plan as "Peri-Approval Submission of Observational Study Reports and Periodic Safety Update Reports." Once the "Peri-approval" time ended, FDA's normal drug oversight programs, funded by regular appropriations, would resume.

In a move that both FDA and the drug industry hope will quicken the drug review process even more, the new performance goal agreement proposes a "first cycle," preliminary review for original NDA/BLA applications. Under this initiative, FDA would give an application an initial quick review and report any significant deficiencies to the drug sponsor. Since this first review would be considered cursory, it would not necessarily be indicative of problems that might arise later in the review cycle. The early feedback provision, like other new initiatives in the proposal, includes additional performance goals for the agency to meet. For example, FDA would have to give sponsors early notifications of deficiencies for 50% of applications in FY2003, 70% in FY2004, and 90% from FY2005 to FY2007.

As in the previous user fee agreements, P.L. 107-188 also requires two annual reports. However, the performance goal report will be submitted to the President and the authorizing committees: the House Energy and Commerce Committee and the Senate Health, Education, Labor and Pensions Committee. The fiscal report is to be submitted to the two authorizing committees.

Tracking PDUFA Activities

Under PDUFA, the FDA uses special time reporting and accounting procedures to track user fee-related work activities performed by its employees.[22] The agency tally the hours reported by FDA staff for human drug review activities and converts them to annual level of effort, expressed as staff "full-time equivalents"(FTEs). The agency then calculates how much it costs for one FTE position to perform one "staff year" of activities.[23] All human drug review activities beyond that paid for the baseline appropriations from general revenues are paid for by PDUFA fees (for PDUFA II, that amount was the FY1997 cost of the drug review adjusted for inflation).

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[22] The FDA also draws a distinction between the time it takes to review a drug application, and the time it takes to approve a new drug. The agency characterizes the time required to review an application, along with related activities, to be part of the overall "review time," some of which is paid for from PDUFA funds. The total approval time is the sum of this review time and any additional time the sponsor of the drug may take to respond to shortcomings in the application identified by the agency. Correcting these problems can often take several "cycles," and this back and forth with the agency can add substantially to a drug's overall approval time.

[23] Suydam, Linda A. U.S. Department of Health Human Services. Federal Drug Administration. Hearings Before the Subcommittee on Health, House Committee on Energy and Commerce. Evaluating the Effectiveness of the FDA Modernization Act of 1997. May 3, 2001.

Prior to PDUFA's enactment in 1992, the FDA had 1,277 FTE employees reviewing drug applications; in FY2002, 3,841 FTE are involved. **Table 3** shows the total number of FTE employees involved with drug and biologics applications review and the FTEs paid by PDUFA fees for FY1998 through FY2002.

Table 3. Comparison of Total FTEs and PDUFA Fee Financed FTEs; FY1998-FY2002, with Request for FY2003

Fiscal year	FDA's total FTEs	Percent change from previous year	Total FTEs in FDA's Human Drug and Biologics Programs	FTEs paid for by PDUFA II fees	PDUFA FTE as a percent of Human Drug and Biologics Programs
1998	9,144	0	3,121	700	22%
1999	8,944	-2%	3,499	729	21%
2000	8,953	0	3,570	951	27%
2001	9,061	1%	3,732	1,082	29%
2002	9,982	10%	3,841	1,102	28%
2003 requested.	10,459	5%	4,200	1,242	30%

Source: U.S. Department of Health and Human Services. Food and Drug Administration. Office of Financial Management. *Justification of Estimates for Appropriation Committees.* Fiscal Years 1999, 2000, 2001, 2002 and 2003. Total program level tables.

PDUFA funds can pay for other regulatory activities if they are part of the application approval process. For example, before final approval of a drug can be granted, FDA must inspect the facility where the drug will be manufactured. This mandatory inspection, for the most part, is treated as part of the overall review and is paid for with PDUFA funds. But if the company asks for an additional inspection before a final approval decision is reached, the inspection is not considered a PDUFA-related activity and would be paid for by appropriated funds. Similarly, the production of FDA's annual performance and financial reports, including efforts to reach PDUFA's performance goals, are both counted as PDUFA-related activities. Also, the agency can use these fees to pay for the monitoring of research conducted in connection with the review of NDAs.[24]

PDUFA's Unintended Consequences

Since PDUFA was enacted, the user fee program has produced some unintended consequences. Many activities that are an integral part of the approval process, such as reviewing investigational new drug applications (INDs) and monitoring clinical trials, are often carried out or completed before the NDA is

[24] FFDCA §735(6)(E). Fees can also be used to pay for administrative costs of the program, leasing and operating facilities and equipment, information management (computers) and advisory committee members' expenses.

submitted and the fee paid. Such regulatory activities are paid for with appropriated funds from general revenues. But there are new regulatory activities included in the performance goals such as initial and follow-up meetings with drug company representatives that have increased in number and scope, but are not sanctioned PDUFA activities in the law, and therefore are not covered by PDUFA fees. At the same time, the number of fee-paying applications has declined along with total PDUFA revenue.[25] Consequently, the PDUFA program has collected fewer funds than the cost of its activities. **Table 4** shows the program costs and receipts as of September 30, 2001 and estimated amounts for FY2002.

Table 4. PDUFA Program Expenditures and Receipts, FY1993-FY2001, Estimate for FY2002

($ in millions)

Fiscal year	Fees spent	Fees collected	Surplus or shortfall
1993	$8.9	$28.5	-$19.6
1994	$40	$53.7	+$13.7
1995	$74.1	$71	-$3.1
1996	$85.1	$82.3	-$2.8
1997	$84.3	$93.2	+$8.9
1998	$101.6	$132.6	+$31
1999	$122.5	$126.6	+$4.1
2000	$147.3	$133.1	-$14.2
2001	$169.1	$135	-$34.1
2002 estimate.	$178.6	$137	-$41.6

Source: U.S. Department of Health and Human Services, Food and Drug Administration, Office of Financial Management, *Justification of Estimates for Appropriation Committees*. Fiscal Years 1999, 2000, 2001, 2002 and 2003.

In addition, the amount collected from NDA/BLA applications makes up one-third of the total fee revenue collected under the program. The other two-thirds come from establishment and product fees. In order to keep the law-mandated proportion, FDA had to charge less for establishment and product fees. This meant that the total fee revenue from the program decreased.

As noted above, the agency received less fee revenue from the program in part because the agency received fewer new drug applications than it had estimated. **Table 5** shows the decrease in the number of all applications filed since 1998. Of all the applications filed, an increased proportion had fees waived. In fact, one source claims that because many more pediatric drug applications were filed under the

[25] DHHS. FDA. FDA's Budget Request for FY2002, *FDA Talk Paper*, T01-12, April 9, 2001.

FDAMA "6-months exclusivity" provision, a total of 35% of all filed applications had their fees waived in 2001.[26]

Table 5. New Drug and Biological Products Filed 1998–2001

Applications filed	Rating	1998	1999	2000	2001
New drug applications filed	Priority	27	31	20	6
	Standard	87	101	88	91
New biological product applications filed	Priority	3	2	4	1
	Standard	5	10	6	6
Total applications filed		**122**	**144**	**118**	**104**

Source: U.S. Department of Health and Human Services. Food and Drug Administration. "New Drug Approval Time: The Facts." Factsheet distributed at an FDA Briefing of PDUFA Performance Goals, March 15, 2002.

Another consequence of the decrease in total program funding is that the agency has had to spend more of its appropriated funds from general revenues on drug review activities than it did in FY1997. This means that the agency has had to shift some of its appropriations from other programs to cover the cost of these activities. The consequence of this shift is that it now takes longer to review applications for generic drugs than it did before 1992, primarily because FDA now devotes fewer resources to this activity.[27]

This is a growing problem, critics say, because the longer it takes to get less expensive generic drugs on the market, the more it costs American consumers and the federal government in terms of health care dollars. Another concern, sometimes voiced by FDA officials, is that the agency may be becoming too dependent on the fees to carry out its normal review activities, at the same time it has to meet more stringent performance goals. In fact, without funds from PDUFA, some believe the agency could not have sustained its current level of drug review activities.[28]

Some FDA personnel closely involved in the review of drug applications have said recently that they sometimes feel unwarranted pressure to do their job as quickly

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[26] Under FDAMA (P.L. 105-115), a manufacturer who submits pediatric studies on drugs available under the Drug Price Competition and Patent Term Restoration Act (known as the Hatch-Waxman Act P.L. 98-417) and the Orphan Drug Act (P.L. 97-414) may receive a 6-month extension of exclusivity or patent protection. The percentage of fees waived came from comments made by FDA officials at a March 15, 2002 presentation on *PDUFA: Financial Aspects*, for Senate staff.

[27] Harris, Gardiner, and Chris Adams. Delayed Reaction: Drug Manufacturers Step Up Legal Attacks that Slow Generics, *The Wall Street Journal*, July 12, 2001, p. A1.

[28] Suydam, Dr. Linda A. The Prescription Drug User Fee Act: An Overview. Presented at a public stakeholders meeting on PDUFA held September 15, 2000. See also: FDA, FY2000 PDUFA Financial Report as required by the Prescription Drug User Fee Act of 1992, as amended by the FDA Modernization Act of 1997, January 2001.

as possible to meet the strict deadlines laid out in PDUFA's annual performance goals. Considering the enormous size and complexity of today's new drug applications, and the time deadlines imposed by PDUFA performance goals, some question whether all of the safety and efficacy data are being evaluated properly.[29] Some even describe the work environment for reviewing drug applications to be somewhat of a "sweatshop," with a level of stress that contributes to staff turnover.[30] Personnel who work in the pre-market drug review area stay with the agency, on average, about 3 years before moving on. Such a turnover rate makes it harder for the agency to maintain the kind of institutional memory needed to evaluate and approve new drugs as quickly as possible.

Legislative Issues

Congress reauthorized the Prescription Drug User Fee Act (PDUFA III) by including it as Title V, Subtitle A -- Prescription Drug User Fees in the conference agreement on H.R. 3448, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188). The conference report was approved by the House of Representatives on May 22, 2002, and by the Senate on May 23, 2002. It was signed into law by President Bush on June 12, 2002.

Congress was acting expeditiously to avoid potential funding interruptions that might have occurred had Congress not acted before August 1, 2002. FDA would have been obligated under the Civil Service Act[31] to begin a reduction-in-force (RIF) process (requiring a 60 day advance notice of the loss of the position) if funding for current positions could not have been guaranteed. This loss of trained reviewers would have greatly affected both the agency and the industry and both worked hard to not let this happen.

PDUFA Legislation in P.L.107-188

The reauthorization legislation aims at rectifying the problem of diminished PDUFA revenues over the last 3 years by restructuring the way FDA's workload is estimated and by setting total fee revenue targets rather than fee rates. The estimated total fee revenue in the legislation for FY2003 is $222.9 million, 38% above the FY2002 fee revenue cap of $161.7 million in current law. **Table 6** shows the total revenue from fee collections for the next 5 years that are authorized in the legislation.

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[29] Meyers, Abbey S. President, the National Organization for Rare Disorders (NORD). House Committee on Energy and Commerce, Subcommittee on Health. Hearings on Evaluating the Effectiveness of the FDA Modernization Act of 1997, May 3, 2001. p. 2.

[30] MacDonald, John A. FDA's Faster Drug Approvals Come at a Cost: Agency Says Emphasis on Speed Leaves Less Money, Time for Critical Safety Reviews, *The Hartford Courant*, December 12, 2000, p. A1. See: FDA/Industry Face-off in Preliminary PDUFA III Discussions, *Inside Washington's FDA Week*, v.7, no.16, April 20, 2001. p. 13-14.

[31] 5 U.S.C. §3502(d)(1)(A) [5 CFR §351.801]

The FY2002 amount is $49.1 million less than the President's FY2003 request of $272 million, in part because the industry balked at paying higher fees.[32]

The PDUFA III legislation eliminated the trigger mechanism set up in PDUFA I and II which say that if the amount FDA spends on drug review is $1 or more below the baseline FY1997 inflation adjusted appropriations, the agency is prohibited from collecting and spending fees for that year. Since the agency does not know the total revenue from the user fees it will collect in any given year (and does not want to lose the program), the agency had spent more from appropriations than it had to on the drug review process each year. The legislation provides FDA with a "margin of error" of up to 5%, and there would be no penalty for underspending by 3% or less. (If FDA underspends between 3% and 5% of the appropriated amount, the agency is required to reduce collections in the following year by the amount in excess of 3%.) The legislation also changes the due date for the product and establishment fees from January 31 to October 1 of the previous year allowing FDA to have the fee revenue earlier.

Table 6. Fee Revenue Amounts for FY2003-FY2007 in P.L. 107-188

($ in thousands)

Type of fee	FY2003	FY2004	FY2005	FY2006	FY2007
Application fee revenue	$74,300	$77,000	$84,000	$86,434	$86,434
Product fee revenue	$74,300	$77,000	$84,000	$86,433	$86,433
Establishment fee revenue	$74,300	$77,000	$84,000	$86,433	$86,433
Total fee revenue	**$222,900**	**$231,000**	**$252,000**	**$259,300**	**$259,300**

Source: U.S. Congress, P.L. 107-188, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, as Title V, Subtitle A – Prescription Drug User Fees, Section 504 (b).

The legislation also revises the definitions of the drug products covered by fees. It allows the Secretary to charge user fees on the products listed in the Orange Book and on biological products listed under Section 351 of the Public Health Service Act.[33] The legislation also eliminates fees for large volume parenteral drug products.[34]

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[32] User Fee Level Funding for PDUFA III Set Lower than Original Bush Budget, *The Pink Sheet*, March 18, 2002, p. 6.

[33] Under current law, any product listed in the "active portion" of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) must pay a product fee. At times, a manufacturer no longer makes a drug and would like to move its listing to the "inactive portion" of the Orange Book and not pay the fee. However, the listing in the book can sometimes be controlled by a re-packer or distributor of a drug rather than by the original sponsor. Unless these people relist the drug, the sponsor of the product still must pay the fee.

[34] Parenteral drugs are substances introduced into the body by intravenous, subcutaneous, (continued...)

The language also eliminates the potential "RIF" problem (see page 14) faced every 5th year of the PDUFA reauthorization cycle. The FDA will be able to increase fees in the final year of the authorization, 2007, so that it will have enough funding to process drug applications for 3 months into FY2008 if there were a delay in the reauthorization of PDUFA at the end of FY2007. In addition, the agency will no longer need to carry over large balances from year-to-year in case the program needs them. PDUFA III's authorization "sunsets" on October 1, 2007.

Congress had concerns about the relationship between FDA and the pharmaceutical industry and the safety of new drugs. A recent article and editorial in the *Journal of the American Medical Association* (JAMA) discusses growing evidence that recently approved drugs are more likely to cause unsuspected serious adverse effects as they are used in this country in a wider population than in the past.[35] In response to these concerns, the legislation adds to the list of activities for which user fees will be used: the collecting, developing, and reviewing of safety information on drugs for 3 years after approval, particularly adverse event reports for drugs approved after October 1, 2002.

Impact of PDUFA

The Pharmaceutical Industry's Views. As noted above, a key issue about the reauthorization of PDUFA was whether the program was needed at all. The U.S. pharmaceutical industry believed that the PDUFA program had been successful, and, as such, was pleased that the legislation passed. Since the law went into effect in 1992, FDA had taken steps to expedite the review process and eliminate the backlog of pending drug and biologic applications. By meeting and consulting with agency officials during the earliest stages of development and testing, pharmaceutical companies gained a better understanding of the kinds of safety and efficacy data the agency was looking for when it evaluated drug applications.[36] According to industry officials, this consultation has led to higher quality drug applications and helped companies reduce the overall cost of research and development. In fact, as discussed above, PDUFA III includes a "first cycle," preliminary review for original NDA/BLA applications whereby the agency will give an application a brief review at a very early stage of its preparation and then report back to the drug sponsor the more significant deficiencies it finds.

The Pharmaceutical Research and Manufacturers of America (PhRMA), the industry's trade association and lobbying group, maintain that under today's more streamlined review system, new drugs are approved in the United States faster than

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[34] (...continued)
or intramuscular injection. The exemption is intended to decrease the administrative burden of determining which products should pay fees.

[35] Lasser, Karen E., Paul D. Allen, Steffie J. Woolhandler, David U. Himmelstein, Sidney M. Wolfe, and David H. Bor. Timing of New Black Box Warnings and Withdrawals for Prescription Medications, *Journal of the American Medical Association*, v.287, no.17, May 1, 2002. p. 2215-2220; and Temple, Robert J. and Martin H. Himmel, Safety of Newly Approved Drugs, *Journal of the American Medical Association*, v. 287, no.17, May 1, 2002. p. 2273-2275.

[36] *Ibid.*

anywhere else in the world. Nonetheless, despite this overall improvement, some drug makers are still concerned about the length of time it takes to get new medicines to market. According to PhRMA, in 2001, member companies received FDA approval for 32 pharmaceutical products - 24 new chemical entities and 8 biologics.[37] Based on its calculations, the 24 approvals were reviewed by FDA in an average of 16.4 months, while the eight biologics were reviewed in an average of 19.6 months. The association found these review times to be a slight improvement over 2000, but noted that review times for both drugs and biologics in 1998 and 1999 were somewhat shorter.[38]

During preliminary discussions about PDUFA's reauthorization, the pharmaceutical industry indicated that it would have been difficult to support any legislative proposal that allowed the use of the user fee money for purposes other than the faster approval of new drugs. During a March 6, 2002 hearing before the House Energy and Commerce Committee, Subcommittee on Health, a brand-name drug industry representative acknowledged that the industry would prefer a reauthorization bill that did not include, for example, statutory language to expedite the approval of generic drugs.[39] Although the final PDUFA reauthorization language does not contain any requirements to assist in the approval process for generic drugs, Section 533 of the bioterrorism legislation, P.L. 107-188, contains authorization for new funding for the Office of Generic Drugs.

At first, the drug industry resisted increasing the agency's post-marketing surveillance activities but finally agreed to the PDUFA III performance goals, made public March 12, 2002, to allow FDA to spend user fee revenues to hire more employees and expand its current post-marketing surveillance activities. These activities are carefully described as having the agency review a company's "proposed risk management plans."[40]

Post-marketing activities described as "collecting, developing, and reviewing the safety information on drugs" have now become part of the sanctioned "process for the review of human drug applications" that can be paid for by PDUFA fees. In addition, the Act amends the FFDCA to require the Secretary to publish on FDA's Internet website a statement about why a sponsor, who received a "fast track"[41] designation for its application, did not complete post-marketing studies to validate the surrogate or clinical endpoint used in the approval of the drug. The Act also requires sponsors who fail to complete timely studies to notify health practitioners of this failure and of unanswered questions related to the clinical benefit and safety of the product.

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[37] Pharmaceutical Companies Made 32 New Treatments Available to Patients in 2001 and Invested an Estimated $30 Billion in R&D. *Pharmaceutical Research and Manufacturers of America*, Press Release, January 25, 2002.

[38] *Ibid.*

[39] U.S. Congress. House Committee on Energy and Commerce, Subcommittee on Health. Hearings on the Reauthorization of the Prescription Drug User Fee Act, March 6, 2002.

[40] *Ibid.*

[41] A "fast track" application is for a product that treats serious or life-threatening conditions and is usually reviewed by FDA in 6 months.

The FDA's Perspective. The FDA maintains that it has successfully met and/or exceeded its performance goals in each fiscal year since 1992. Not surprisingly, the agency supported the reauthorization of the user fee program since it provides additional funds to deal with various operational concerns. For example, since PDUFA began, FDA has developed a computerized tracking system that allows it to manage the review of drug applications. In addition, the agency has now standardized the medical and statistical information that needs to be included with NDAs, and routinely accepts data submitted electronically on behalf of drug applications. Some of the success in meeting PDUFA's performance goals is, the agency admits, also attributable to the higher quality of the applications submitted today by drug companies.

In 2001, FDA's Center for Drug Evaluation and Research (CDER) approved a total of 66 new drug products, 24 of which were new molecular entities (NMEs[42]), three fewer than the agency approved the year before. According to FDA, 10 of the 66 new drugs (seven of the NMEs) received priority status and were reviewed and approved in the median time of 6 months. The other 56 drugs, with standard status, were approved in the median time of 12 months (15.7 months for the standard NMEs), and their median total approval time was 14 months (19 months for the NMEs).[43]

Although PhRMA found review times in 2001 to be less than in 2000, a recent article regarding FDA's most recent drug approval numbers stated that the review times for 2001 were higher than for 2000, in part because FDA required brand-name drug companies to respond to requests for more information on several NMEs. There also was a decline in the number of applications judged "priority" which get faster attention.[44] The assessment concluded, however, that the 2001 numbers suggested that the shorter review deadlines set by the 1997 PDUFA II performance goals were not necessarily translating into faster overall approval times.[45]

The number of new drugs that FDA approves each year is an ongoing issue, for both the pharmaceutical industry and the agency turn to the numbers as a measure of timeliness and productivity. Whether the numbers actually say anything about the interplay between regulation and pharmaceutical R&D raises questions. Nevertheless, in the long running debate about whether new pharmaceuticals are being approved fast enough in this country, both industry and government use the figures to support their positions.

Since the PDUFA era began in 1992, the FDA has approved, on average, slightly more than 30 new molecular entities per year; the smallest number of

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[42] New Molecular Entity (NME) refers to a new, chemically unique compound that is different from the other drugs already on the market. NMEs also contain active substances that has never been approved for marketing in any form in the United States.

[43] EHS. FDA. Activities of FDA's Medical Product Centers in 2001. *FDA Talk Paper*, January 25, 2002.

[44] FDA Drug Approval Times Edges Up to 18.5 Months in 2001. *The Pink Sheet*, January 7, 2002. p. 12.

[45] *Ibid.*

approvals was 22 in 1994, and the largest was 53 in 1996. Regardless of how many drugs are approved each year, the data from such a small sample size can lead to unfounded conclusions for several reasons. First, in any given year the number of new compounds in the drug industry's R&D pipeline will vary. Therefore, fewer drug applications may be filed with the FDA from one year to the next. In addition, the number of drugs classified as priority by FDA will change year-by-year. Also, in some cases the review of a drug application is stopped until the sponsor of the NDA comes up with the information or data the FDA needs to complete the review. All of these variations will affect the number of drugs approved in ways that are likely to be independent of any PDUFA factors.

Consumer views on PDUFA. Generally, consumer and patient advocacy groups[46] applaud the fact that the additional money from PDUFA has hastened the availability of new medicines. However, some groups expressed concern that FDA has become much too dependent on the user fees, and that this could lead to conflicts of interest.[47] From their perspective, the review of drug applications is a regulatory responsibility that should be shouldered completely by the federal government. They argue that rather than relying on the help of user fees, Congress should instead appropriate the full amount of money necessary to support FDA's primary mission. Further, they are concerned that the user fee law's successes may be undercutting congressional support for increases in FDA's budget. In fact, a patient coalition claims that under the new law, the drug industry could pay 51% of the cost of the review, with appropriations providing 49%. They argue that if the drug industry were to pay 51% of the cost of the review, there could be conflict-of-interest questions about agency actions.[48] These consumer groups also worry that PDUFA gives the pharmaceutical industry more influence over setting performance goals and other regulatory priorities than is justified for a regulated industry. Former FDA Commissioner Dr. Jane Henney has said that while there is no evidence that the PDUFA program has compromised the agency's independence and objectivity, even the perception of a conflict-of-interest, or an emphasis on numbers, could be "worrisome" since it might threaten consumer confidence in FDA reviews.[49]

The reauthorizing legislation answered some criticisms about the non-transparency of negotiations on performance goals. It requires the Secretary to consult with the authorizing committees, and representatives of the science, academic, health care, patients, consumers, and pharmaceutical communities in developing recommendations for performance goals. Once these goals are formulated, the Secretary is to publish them in the *Federal Register*, present them to

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[46] Consumer groups participating in the September 15, 2000 stakeholders meeting included the National Women's Health Network, Public Citizen, the National Consumer League, and the Center for Medical Consumers.

[47] Plunkett, Travis B. Hearings Before the Subcommittee on Health, House Committee on Energy and Commerce. *Evaluating the Effectiveness of the Food and Drug Administration Modernization Act of 1997*, May 3, 2001. p. 6-7.

[48] Patient and Consumer Coalition, *Secret FDA/Industry Agreement Has Serious Flaws for Patients and Consumers*, unpublished position paper, March 29, 2002.

[49] Henney: FDA Staffing, PDUFA, International Agreements, Future Hot Button Issues, *Inside Washington's FDA Week*, v. 7, no. 24, June 15, 2001. p. 15-17.

the congressional authorizing committees, hold a public meeting to discuss them, and provide a "30-day comment period" for public comment.

Some critics also charge that expecting the FDA to meet or exceed PDUFA's performance goals every year is misguided since reaching the goals contributes more to drug maker's revenues than it does to the betterment of consumer health. Moreover, they are concerned that the number of prescription drugs recently withdrawn from the market threatens public confidence in the way the agency evaluates the safety and effectiveness of pharmaceuticals. These critics have suggested that recent withdrawals show that the drugs were unsafe and should not have been approved in the first place.[50]

Some groups worry that FDA treats as equally important, applications for beneficial breakthrough therapies, as it does those for so-called "me-too[51]" or "lifestyle" drugs.[52] These groups would like to see FDA make a distinction between these categories when it calculates review times, and would much prefer that the agency look at a new drug's contribution to public health, rather than completed review numbers, as a better measure of success.

Should User Fees be Expanded to Other Products?

During the debate over PDUFA's reauthorization, some stakeholders urged Congress to let FDA assess user fees for other products, particularly for the quicker approval of less expensive generic drugs. In years past, makers of generic drugs have held somewhat discordant views on the idea of paying user fees for their products. Some manufacturers feel that the additional revenues will translate into faster approval times, as it has for the makers of brand name drugs. Others, however, are not sure they want to pay money for something that is now free of charge. Still others express concerns about maneuvers of the brand-name drug companies to delay the marketing of generic drugs.[53] Congress did not add generic drugs to the list of products covered by user fees, but it did authorize in the law additional funds for the Office of Generic Drugs. From the FY 2003 appropriated amounts for FDA, the Office is authorized to receive an increase of $3 million; for FY2004, an increase of

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[50] Lasser, Karen E., Paul D. Allen, Steffie J. Woolhandler, David U. Himmelstein, Sidney M. Wolfe, and David H. Bor. Timing of New Black Box Warnings and Withdrawals for Prescription Medications, *Journal of the American Medical Association*, v.287, no.17, May 1, 2002, pp. 2215-2220; and Temple, Robert J., and Martin H. Himmel, Safety of Newly Approved Drugs, *Journal of the American Medical Association*, v. 287, no.17, May 1, 2002. p. 2273-2275.

[51] "Me Too Drugs" are drugs closely related to another drug on the market, in terms of its chemical structure. Such drugs are designed to enhance or at least mimic the effects of an existing drug in a therapeutic category, in an effort to achieve market share.

[52] "Lifestyle drugs" are drugs developed to enhance the quality of life, not to treat an illness or disease. Lasser, op cit.

[53] Some of the maneuvers consist of numerous citizen's petitions, unwarranted patent extensions, and the last minute listing of new patents by brand name manufacturers in FDA's Orange Book. All these actions make it harder for generic drugs to gain market entry. Harris, Gardiner, and Chris Adams. Delayed Reaction: Drug Manufacturers Step Up Legal Attacks that Slow Generics, *The Wall Street Journal*, July 12, 2001. p. A1.

$6 million; for FY2005, an increase of $9 million; for FY2006 an increase of $12 million; and for FY2007, an increase of $15 million.

Others are suggesting that Congress authorize the collection of user fees to speed up the review and approval of medical devices. However, the three largest trade associations that represent most of the medical device industry have lobbied for years against user fees, maintaining that approval of devices is a public health activity.[54] According to the associations, Congress should appropriate enough money to cover this regulatory activity rather that make the industry pick up some of the cost.[55] However, several association dropped their objections. On October 2, 2002, the House Energy and Commerce Committee passed Amendment in the Nature of a Substitute to H.R. 3580, the Medical Device User Fee and Modernization Act of 2002. It would establish a device user fee program, require labeling of reprocessed devices, allow third-party inspections of device manufacturers, and establish a new FDA Office of Combination Products. The Senate has not yet taken up a similar measure.

Reportedly, animal drug manufacturers were also interested in paying for more timely product reviews under PDUFA, but were unsuccessful in extending coverage in this legislation. Many pharmaceutical companies that produce human drugs also make animal drugs for use in agriculture and veterinary medicine. According to some reports, workload increases, coupled with decreases in the number of staff in FDA's Center for Veterinary Medicine, have recently slowed the review of New Animal Drug Applications (NADAs), abbreviated NADAs, and the testing of new animal drugs.[56] For these reasons, some animal drug makers are continuing to seek user fees as one way to accelerate regulatory review of their products.

Increasing Appropriations for Other Regulatory Activities

P.L. 107-188 authorizes FDA to spend PDUFA revenues on the monitoring of product safety.[57] (See above page 17.) One reason to include this new authorization was that the conferees wanted the agency to increase its post-marketing surveillance for all pharmaceuticals, but especially those that have been recently approved for marketing.[58] Such increased surveillance could lead to the earlier detection of unanticipated side-effects which often do not show up until the drug has been prescribed for a large patient population. More oversight effort may also lead to better management of these adverse reactions by doctors and other health care

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[54] Advanced Medical Technology Association (AdvaMed); Medical Device Manufacturing Association (MDMA); and the National Electrical Manufacturing Association (NEMA).

[55] Administration Floats Device User Fees in Meeting with Device Firms, *Inside Washington's FDA Week*, v.7, no. 14, April 6, 2001.

[56] FDA, Animal Drug Industry Reach Pact on Animal Drug User Fees, *Inside Washington's FDA Week*, v.8, no.8, February 22, 2002.

[57] Axelrad, Jane A. Associate Director for Policy. Center for Drug Evaluation and Research. Food and Drug Administration. *CDER Update*, speech presented at the Food and Drug Law Institute Annual Educational Conference, April 18, 2001.

[58] FDA Reviewer Retention Remains Priority in FY2001-User Fee Report, *The Pink Sheet*, February 5, 2001. p. 25.

providers by giving them the timely, accurate medical information they need to make informed intervention or prescribing decisions. To fund these added activities, P.L. 107-188 contains authorization for additional funds from the FY2003 appropriated funding for FDA and the Office of Drug Safety. The legislation authorizes additional $5 million for FY2003; $10 million for FY2004; and at least $10 million for FY2005, FY2006, and FY2007 with adjustments made for inflation.

In the debate over the reauthorization, concerns were raised about the amount of direct-to-consumer (DTC) advertising of prescription drugs and its effects on consumers. Some critics wanted Congress to give the FDA broader regulatory authority in this area. Section 201 of the FFDCA currently gives the agency the authority to consider as misbranded any drug whose labeling or advertising is false or misleading in any way.[59] However, the law prohibits the FDA from issuing any rules that would require prior approval of the content of a company's prescription drug advertising. Despite these constraints, the agency does ask companies to submit promotional materials that will be used when the product is first introduced into the market.[60] Although the agency has *no pre approval* authority over drug advertising, it does get involved whenever companies submit draft materials for the agency's review and comment before the ad airs on TV and radio. Nevertheless, DTC advertising for prescription drugs grows more prolific every day. Some feel that FDA should have the authority to take a closer look at these ads and that user fee revenues be used for this purpose.[61] In support of FDA's current activity in this area, Section 522 of P.L. 107-188 authorizes increases of $2.5 million for FY2003, $4 million for FY2004, $5.5 million for FY2005, $7.5 million for FY2006, and $7.5 million for FY2007 from FY2003 appropriated funding for FDA and the Office of Medical Policy (Division of Drug Marketing, Advertising, and Communications – DDMAC), FDA's division that monitors DTC advertising. The funds are to ensure that promotional drug material is not false or misleading.

Conclusion

As Congress took up the reauthorization of PDUFA, it faced differing questions and opinions on how the user fee revenues should be spent. Under PDUFA I and II, new drugs and biological products are approved in the United States faster than in the years preceding 1992. Today, the FDA considers the fee revenue it gains as necessary for staff retention, and for maintaining its expert science base. With this reauthorization, the agency will increase the fee revenues available for drug application reviews and institute several new regulatory initiatives. The pharmaceutical industry is supportive of PDUFA's reauthorization. Some consumers, however, while supporting the availability of new drugs, have expressed concern over whether drugs are being reviewed too quickly thereby raising questions

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[59] 21 U.S.C., Section 502 (n). Advertising for over-the-counter drugs is regulated under different statutes by the Federal Trade Commission.

[60] 21 C.F.R. 314.81(b)(3)(i)states: "The applicant shall submit specimens of mailing pieces and any other labeling at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product."

[61] Patient and Consumer Coalition. *Secret FDA/Industry Agreement Has Serious Flaws for Patients and Consumers*, unpublished position paper, March 29, 2002.

about safety. They suggest that even with expanded authorization for funding of FDA's post market surveillance programs to monitor adverse reactions to drugs, the language in the PDUFA reauthorization to disclose and notify practitioners of incomplete post-approval studies, there are lingering safety issues unaddressed. However, the support in Congress for PDUFA reauthorization was almost unanimous