EXHIBIT 3
(Part 1 of 2)

White Paper
Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications

Executive Summary

The Prescription Drug User Fee Act (PDUFA) program is the cornerstone of modern FDA drug review. User fees currently fund about half of new drug review costs. By providing needed funds, PDUFA ended slow and unpredictable review and approval of new drug applications, while keeping FDA's high standards.

PDUFA funds allowed FDA to accomplish a number of important goals. FDA hired more review and support staff to speed review. The number of full-time equivalent (FTE) staff devoted to the new drug review process has nearly doubled, growing from 1,277 FTE in 1992 to 2,503 FTE in 2004. FDA upgraded its data systems and gave industry guidance to help minimize unnecessary trials and generally improve drug development. FDA gave industry guidance on how to improve the quality of applications, with the goal to reduce misunderstandings and the need for sponsors to rework and resubmit applications. Finally, FDA improved procedures and standards to make review more rigorous, consistent, and predictable. [Section 1]

Taken together, all of these steps ensure that the time and effort patients put into clinical tria ls provide useful data. They also lowered drug development costs and shortened review times. For example, the median approval time for priority new drug applications and biologics license applications decreased from 13.2 months in 1993 to 6.4 months in 2003. Ultimately, these developments enabled FDA to ensure that needy American patients get fast access to novel drugs—faster, in fact, than citizens of other countries. Since the start of PDUFA, FDA has approved over 1,000 new drugs and about 100 new biologics. Under the currently authorized program (PDUFA 3) 50 percent of new drugs are launched first in the United States, compared to only 8 percent in the years pre-PDUFA.

To get to these outcomes, PDUFA established goals acceptable to FDA and new drug sponsors for both reviewing drugs and giving industry guidance during drug development. These goals included the following. [Section 3]

- Review standard and priority applications within specified time frames in a manner that balances the preservation of review process integrity with "fast as possible" patient access to needed treatments.
- Quickly review sponsors' appeals to FDA decisions to place "holds" on conducting clinical trials.
- Give early feedback, when requested, on certain types of clinical studies ("special protocol assessments") to promote rapid and cost-effective drug development.
- Quickly respond to and schedule sponsor-requested meetings to promote rapid and cost-effective drug development.
- Facilitate guidance development on good review practices.
- Implement and evaluate pilot projects to test various alternatives for expediting drug review without sacrificing drug safety.

Additional goals specifically focused on preserving an appropriate balance between drug efficacy and drug safety by funding safety-related activities for the first 2 years of product marketing for most drugs,

and the first 3 years for potentially dangerous drugs. PDUFA fees also enabled FDA to issue guidance for FDA and industry on how best to assess, manage, and monitor drug risk. [Sections 3.4-3.5]

However, since the PDUFA program began, FDA's drug review workload substantially increased. [Section 4]

- Original drug and biologic applications submitted for review increased by over 50 percent between Fiscal Year (FY) 1993 and FY 2004. This increase occurred primarily for drug, as opposed to biologic, applications. Overall, most applications are for drugs.
- Efficacy supplements submitted for review increased by more than 80 percent between FY 1993 and FY 2004. As with original applications, most submissions are for drugs.
- Chemistry, Manufacturing and Controls (CMC) supplements submitted for review doubled between FY1993 and FY2004. Biologic CMC submissions increased more than 4-fold.
- Sponsor-requested meetings held since specific PDUFA goals were established increased by about one-third (FY1999-FY2004). FDA holds an average of 9 sponsor-requested meetings every business day.
- Requests submitted for special clinical protocol reviews increased almost 5-fold between FY1999 and FY2004.
- FDA responses to appeals from sponsors over "holds" on their clinical trials more than tripled between FY1998 and FY2004.
- Serious adverse events drug sponsors reported sponsors to FDA increased almost 9-fold between 1992 and 2004. Americans received over 80 percent more prescriptions by the end of that time frame as they had at the beginning.

At the same time that workload has increased, FDA's capacity to deliver timely and predictable performance is challenged by cost pressures, budget constraints and the need to meet other important work mandates. These challenges have been accompanied by flat to negative growth of total appropriated funds to FDA. The challenges include: mandated federal pay increases and earmarks for important non-PDUFA programs including activities around generic drugs, blood safety, and influenza vaccine; the costs of recruiting and retaining qualified expert (marketable) reviewers; and normal market-driven increases in the cost of facility upkeep and rent for necessary work space. [Section 5]

Introduction

The Prescription Drug User Fee Act (PDUFA), which authorizes FDA to collect user fees amounting to a little more than half of total funding for drug review, expires in September 2007. Without further legislation, FDA would be unable to collect user fees for the new prescription drug review program. This paper provides data and information on the scope and current status of FDA's program to implement PDUFA, so as to inform public discussions regarding PDUFA reauthorization.

PDUFA has had a significant role in modern drug review at FDA. It has been a key to ending major problems with unpredictable and slow review and approval of new drug applications. It has provided funds to eliminate or even reversed the so-called "drug lag" attributed to inadequate staff and computer resources. Americans now get access to more new medicines faster than patients in other countries, while prior to PDUFA, American patients waited for FDA to act long after new drugs were available in Europe.

Reauthorization of PDUFA in 1997 (PDUFA 2) and 2002 (PDUFA 3) established a precedent for a process to identify areas to consider related to PDUFA 4 in 2007. FDA seeks public comment on the current program, including views on what features should be retained and what might be done to further strengthen and improve the program. On November 14, 2005, FDA will hold a public meeting on PDUFA http://www.fda.gov/oc/meetings/pdufa111405.html and will at the same time open a public docket http://www.fda.gov/OHRMS/DOCKETS/98fr/05-20875.htm. where people can submit written comments. In addition, per provisions of the statute, the Secretary of DHHS will consult with the Committee on Energy and Commerce of the House of Representatives, the Committee on Health, Education, Labor, and Pensions of the Senate, appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry. The Secretary will publish in the Federal Register any recommendations after negotiations with the regulated industry and will present the recommendations to the congressional committees. In addition, the Secretary will publish a Federal Register notice including department recommendations to Congress regarding PDUFA reauthorization. Following that FR notice, FDA will hold another public meeting to hold a meeting at which the public may present its views on those recommendations; and will provide for a period of 30 days for the public to provide written comments on those recommendations.

This white paper summarizes major factors behind establishment of the program. The paper describes how the fees are collected and what they pay for, and how the PDUFA program has evolved since its enactment in 1992. In addition, the paper describes progress to date, and current challenges for the funding of drug review and achieving the related public health aims.

- Section 1 highlights major factors that resulted in the enactment of the Prescription Drug User Fee Act (PDUFA).
- Section 2 outlines how the PDUFA user fees are structured and collected and summarizes the current level of fee collections.
- Section 3 describes the scope of regulatory activities supported by PDUFA fees, and explains how these activities help to speed access to safe and effective new drugs.
- Section 4 describes how the PDUFA program has evolved and how the associated review workload has grown since its first enactment in 1992.
- Section 5 concludes with a summary of key challenges for FDA related to PDUFA and new drug review.

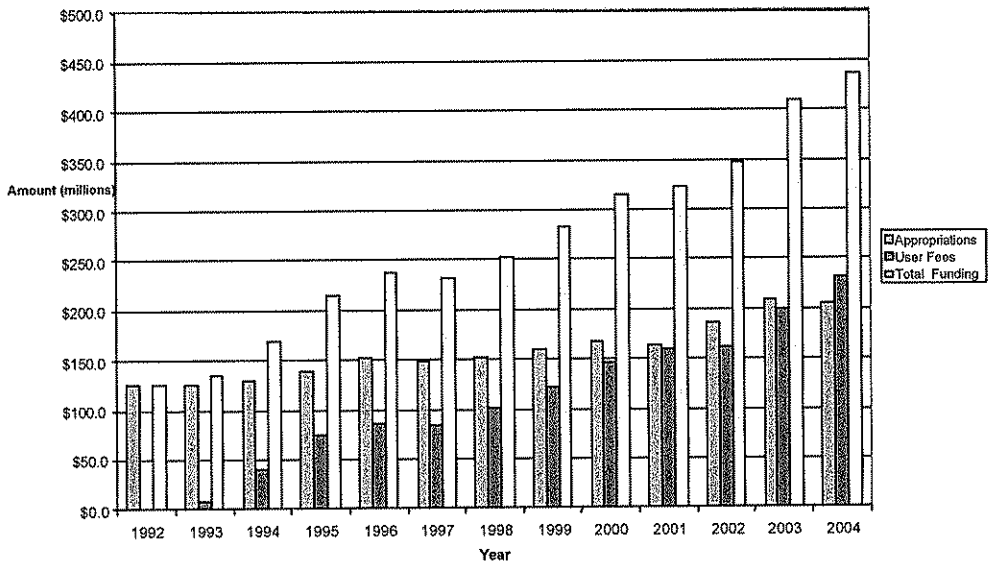
1. Major Factors Resulting in Enactment of PDUFA in 1992

Drug review at FDA prior to PDUFA entailed a variety of problems that PDUFA alleviated. Before PDUFA, FDA's review process was understaffed, unpredictable and slow. FDA lacked sufficient staff to perform timely reviews, or develop procedures and standards to make the process more rigorous, consistent and predictable. FDA lacked the funds to provide computers to all FDA reviewers. At the same time, regulators in other countries were able to review products faster. Access to new medicines for U.S. patients lagged behind. For example, U.S. patients were not getting access to new AIDS drugs as quickly as in other countries. Chronic understaffing of drug review, and related delays in U.S. patient access to new drugs led to the 1992 enactment of PDUFA.

PDUFA was established to increase FDA funding for human drug review and to increase the speed and predictability of the review process. Under PDUFA the U.S. pharmaceutical and biotechnology industries would pay user fees and FDA would commit to develop a more standardized process and faster, more predictable review timeframes. (Section 4 provides more details on the performance goals related to these commitments.) PDUFA provided FDA with added funds that enabled the agency to hire additional reviewers and support staff and upgrade its information technology systems to speed up the application review process for new drugs and biological products without compromising FDA's high standards for approval.

Since the beginning of the program, there has been a significant improvement in FDA funding for the drug review program, including significant investments in information technology. As shown in Figure 1.1, PDUFA has enabled the nominal funding for human drug review to increase by over 225 percent from 1992 to 2004. Because Congressional appropriations have grown at a much lower rate, user fees now represent over half of all resources devoted to the review of human drugs.

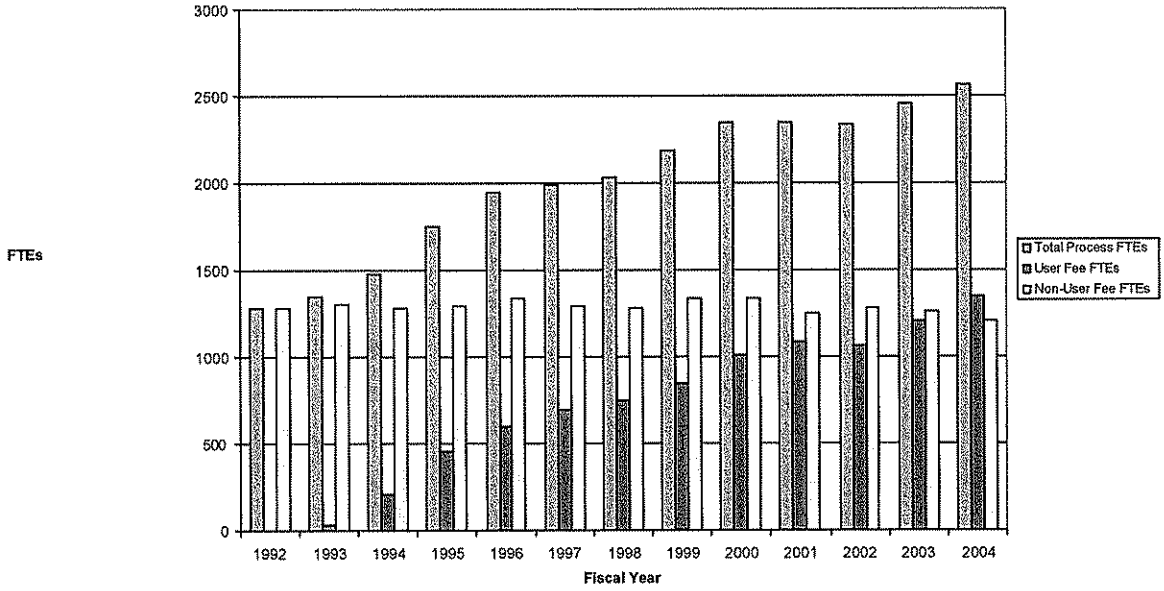
Figure 1.1 History of Funding for Review of Human Drugs



PDUFA has resulted in a significant increase in staffing, enabling FDA to provide more guidance for industry during drug development and improvements to the review process. As shown in Figure 1.2, the

number of full-time equivalent staff (FTEs) devoted to the new drug review process nearly doubled between 1992 and 2004, increasing from 1,277 FTEs in 1992 to 2,503 in 2004. The increased share of program support from user fees means that currently more than half of all FTEs devoted to the review of human drugs are now funded by user fee revenues.

Figure 1.2 History of PDUFA Total Process and User Fee Funded FTEs

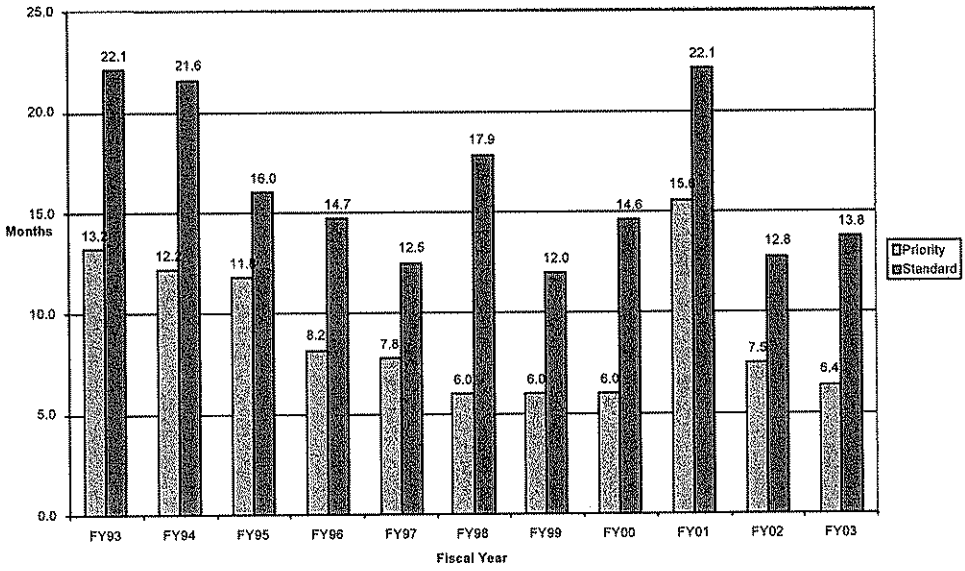


FDA committed to certain performance goals on timeframes for the review of new drug applications (NDAs) and biologics license applications (BLAs). FDA has met or exceeded all PDUFA NDA and BLA review goals since PDUFA's inception.
However, meeting review goals is not the only desired outcome. By meeting the review goals, FDA has been able to dramatically reduce the time to approval for new drugs and biologics and provide the American public with access to these medical treatments more quickly.

Since the start of PDUFA, FDA has approved 1,010 new drug applications and about 100 biologics licensing applications. These include 62 new cancer drugs, 109 new drugs for metabolic and endocrine disorders, 96 new anti-infective drugs, 103 new drugs to treat neurologic and psychiatric disorders and 73 new drugs to treat cardiovascular and renal disease.

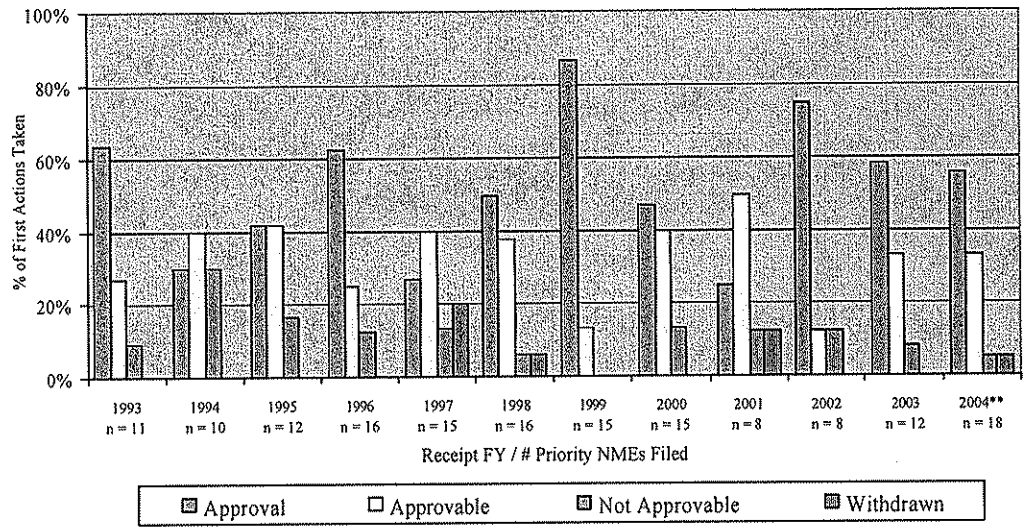
Between 1993 and 2003 the median approval time for priority NDAs and BLAs decreased by over half -- from 13.2 months in 1993 to 6.4 months in 2003. Over this same time period the median approval time for standard NDAs and BLAs decreased by over one third, from 22.1 months in 1993 to 13.8 months in 2003. Figure 1.3 shows the median approval times for NDAs and BLAs by priority status for the PDUFA era, and depicts the overall trend toward shorter times to new drug approval for both priority and standard drug applications.

Figure 1.3 Median Approval Times for NDAs and BLAs



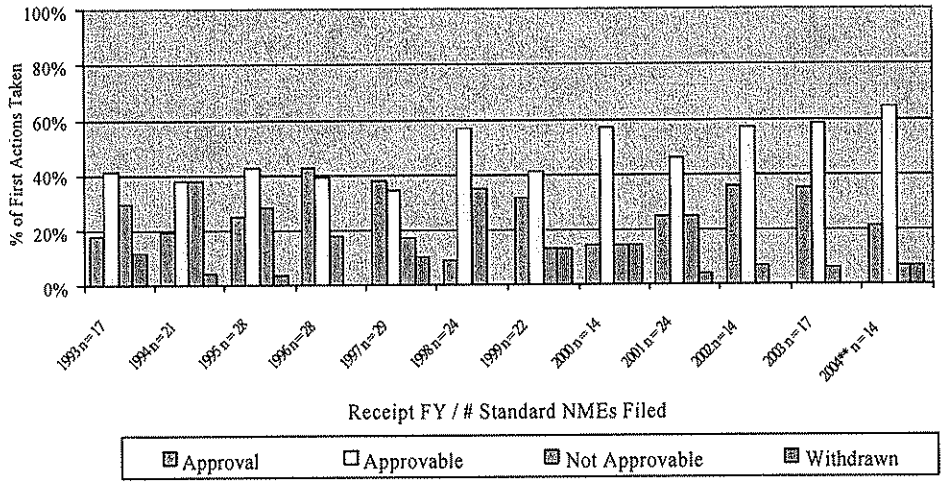
The reduction in median approval times has resulted from significant improvements in FDA review process efficiencies, while holding to the same high standard of evidence for drug safety and effectiveness. This is evident in the data showing the percentage of applications approved on the first cycle [i.e., the first time they are submitted for FDA review] versus approved on a subsequent review cycle after they have successfully addressed deficiencies identified by FDA in a previous review. As shown in Figures 1.4 the percentage of priority applications approved on first cycle has changed very little over the years, even as the median approval times have declined.

Figure 1.4 First Action Percentages for CDER Priority NMEs and New BLAs by Fiscal Year of Receipt



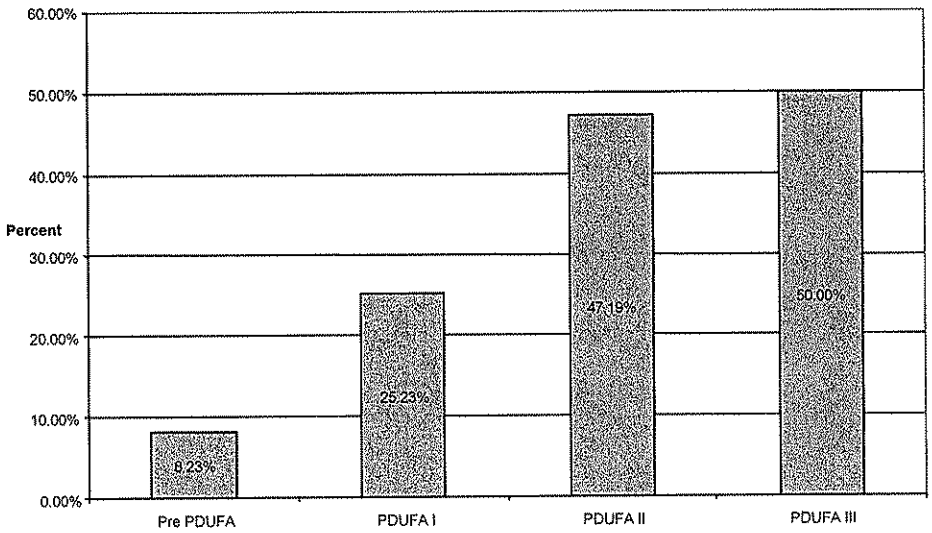
The data for percentage of first versus later-cycle approvals for standard drug applications also suggest that there is no trend toward increasing approvals in the first cycle. However, as shown in Figure 1.5, the data do suggest that an increasing percentage of sponsors are effectively addressing deficiencies identified in the first cycle, and are able to obtain approval after the second cycle of review.

Figure 1.5 First Action Percentages for CDER Standard NMEs and New BLAs by Fiscal Year of Receipt



The combination of realistic time frames, management improvements, and additional resources improved FDA's review performance for drugs and biologics. Since the start of PDUFA, the so-called drug lag in America, compared to other countries, has been reversed and the proportion of all new drugs first marketed in the United States has increased dramatically. Figure 1.6 shows the percent of new chemical entities (NCEs)/new active substances (NASs) first launched in the United States: pre-PDUFA period of 1980-1992, PDUFA 1 years 1993-1997, PDUFA 2 years 1998-2002 and PDUFA 3 2003-2004.

Figure 1.6 Percent of NCEs/NASs First Launched in US 1980 through 2004 by PDUFA Cohort



2. PDUFA Financing of New Drug Review

The design of PDUFA user fees detailed in the provisions of the statute, has contributed to the program's stability and success. This section reports on the design and the current level of fee collections.

PDUFA fees are collected in three components: application fees, establishment fees, and product fees. Each of the three types of fees contributes one third of the total revenues in a fiscal year. An application fee must be submitted when certain new drug applications (NDAs) or biologic license applications (BLAs) are submitted. Product and establishment fees are due annually on October 1. The total revenue amounts derived from each of the categories—application fees, product fees, and establishment fees—are set by the statute for each fiscal year. The following schedule was included in PDUFA 3:

``Type of Fee Revenue	Fiscal Year 2003	Fiscal Year 2004	Fiscal Year 2005	Fiscal Year 2006	Fiscal Year 2007
Application/Supplement.....	$74,300,000	$77,000,000	$84,000,000	$86,434,000	$86,434,000
Establishment.....	$74,300,000	$77,000,000	$84,000,000	$86,433,000	$86,433,000
Product.....	$74,300,000	$77,000,000	$84,000,000	$86,433,000	$86,433,000
Total Fee Revenue.....	$222,900,000	$231,000,000	$252,000,000	$259,300,000	$259,300,000

The increase in revenues each year was provided to give FDA sufficient resources to meet the performance goals that are also agreed to over the 5 years of the program.

PDUFA authorizes adjustments in fees to account for cost inflation and workload changes. The statutory amounts shown in the box above must be adjusted for cumulative inflation since FY 2003 and for changes in drug review workload in each fiscal year. PDUFA 3 authorizes FDA in each fiscal year to set user fees so the total revenue that FDA receives from each fee category approximates the statutory amounts, after the adjustments for inflation and the workload. Those fees, with the rational for their calculation, are

published in the Federal Register each year in early August before the beginning of the Fiscal year on October 1. The fees for the first 4 years of PDUFA 3 are shown in the table below.

	FY 2003	FY 2004	FY 2005	FY 2006
Application Fee	$533,400	$573,500	$672,000	$767,400
Establishment Fee	$209,900	$226,800	$262,200	$264,000
Product Fee	$32,400	$36,080	$41,710	$42,130

The fees for applications have risen faster than the other fees because the estimate of the number of full applications fees that FDA will receive, and that will produce the revenue expected, has gone down from an estimated 139 in 2003 to an estimated 129 in 2006. (It should be noted that about 25 percent of all applications received each year do not pay fees because the applications are for fee-exempt orphan products, or the fees are waived either because it is the first application from an small business or it qualifies for one of the other waiver provisions. The estimates of the numbers of fees that will be received is based on a rolling average of the number of full application fees received in the previous 5 fiscal years.)

PDUFA has provisions intended to ensure that the resources from user fees are in addition to and not instead of Congressional appropriations to support the process of human drug review. It imposes three legal conditions on FDA's authority to collect the user fees.

1. FDA's overall Salaries and Expenses Appropriation (excluding user fees) must meet or exceed FDA's overall FY 1997 Salaries and Expenses Appropriation (excluding user fees and adjusted for inflation).
2. The amount of user fees collected in each year must be specified in Appropriation Acts.
3. FDA may collect and spend user fees only in years when FDA also uses a specified minimum amount of appropriated funds for the review of human drug applications. The specified minimum is the amount FDA spent on the review of human drug applications from appropriations (exclusive of user fees) in FY 1997, adjusted for inflation.

So far, FDA has been able to meet these three conditions.

FDA administration of fee collections is designed to ensure both efficiency and complete separation of fee collections from fee-supported review activities. The collection of fees for applications is done through Mellon Bank and coordinated by FDA's Office of Financial Management in the FDA Office of Commissioner. The annual bills for establishment fees and product fees are based on FDA's database of listed products and active establishments, and fee monies are then collected centrally by Mellon Bank. FDA drug reviewers and other staff are generally unaware of whether and how much any individual company has paid in user fees. The table below summarizes fee collections for the most recently available Fiscal Years 2003 and 2004.

FDA Statement of User Fee Revenues by Fee Source
As of September 30, 2004

Fee Category	FY 2003	FY 2004
Fees Collected:		
Product Fees	$76,852,785	$76,453,520
Establishment Fees	$78,209,219	$82,318,894
Application Fees	$62,684,550	$87,693,991
Total Fees Collected:	**$217,746,554**	**$246,466,405**

FDA spends user fee revenues only on activities to support the "process for the review of human drug applications"[1], as defined in PDUFA 3. Under PDUFA, fees collected and appropriated, but not spent by the end of a fiscal year, continue to remain available for FDA to spend in future fiscal years. In FY 2004, FDA obligated $232,081,500 from user fee revenues. Those costs were distributed as shown in the table below. The amounts are based upon the obligations recorded as of the end of each fiscal year. In the past, over 81 percent of amounts obligated are expended within one year, and 96 percent within two years. Thus, annual obligations represent an accurate measure of annual costs.

FDA Process for the Review of Human Drug Applications – Total Costs
As of September 30, 2004

FDA Component	FY 2003	FY 2004
Center for Drug Evaluation and Research (CDER)	$250,370,170	$293,991,408
Center for Biologics Evaluation and Research (CBER)	$110,132,866	$91,905,443
Field Inspection and Investigation Costs (ORA)	$19,098,382	$19,646,087
Agency General and Administrative Costs (OC)	$29,840,492	$31,313,598
Total Process Cost	**$409,441,910**	**$436,856,536**
Amount from Appropriations	$$209,287,410	$$204,775,036
Amount from Fees	$200,154,500	$232,081,500

The costs for all components, except for CBER, rose in FY 2004. The increased expenditures primarily reflect the additional personnel hired by the organizations in FY 2004 and the mandatory pay raise for all federal employees. The reason for the decrease in CBER and the increase in CDER is because of the transfer of review responsibility for certain therapeutic biologics from CBER to CDER in FY 2004. The methodology used to develop the estimated full cost of human drug review is detailed in Appendix D of the FY 2004 PDUFA Financial Report www.fda.gov/oc/pdufa/finreport2004/default.htm.

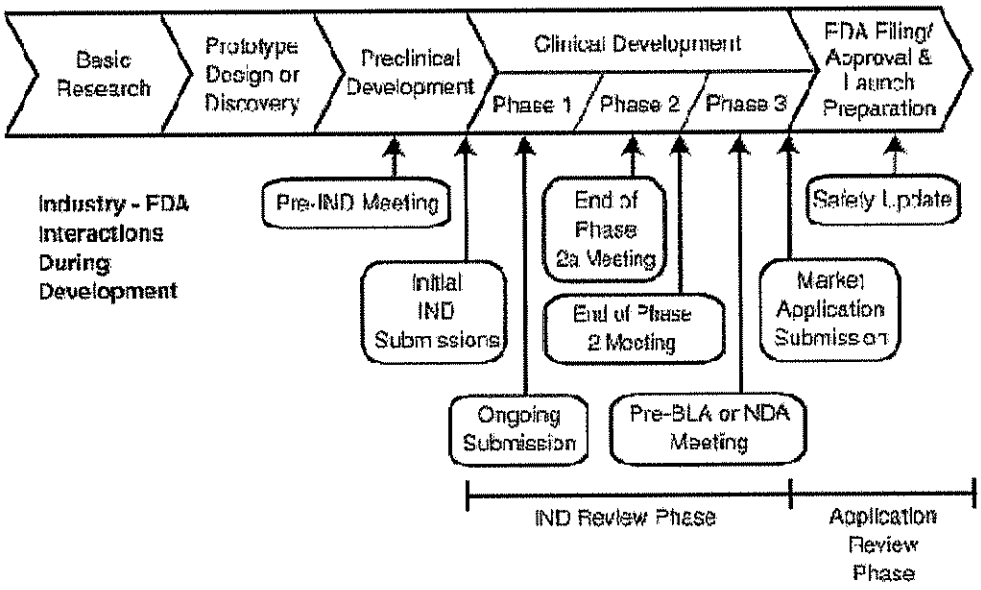
3. Scope and Importance of PDUFA-Supported Work

The activities encompassed in the PDUFA "process of human drug review," that are needed to improve drug development and speed patient access, begin well before a product sponsor submits a new drug application for FDA pre-market review. Although not often discussed, these other—often FDA labor-intensive—activities are critical to improving the quality of a sponsor's drug development and the quality of a submitted market application. High-quality development is crucial to patient safety during clinical trials and to ultimate approval of a safe and effective product. Application quality is a decisive factor in drug review and approval.

PDUFA funding has enabled increased review staffing to increase FDA-sponsor interactions for scientific and regulatory consultation at a number of critical milestones in drug development, as shown in Figure 3.1.

[1] Discussion of the PDUFA definition of the "process of review of human drug applications" can be found at http://www.fda.gov/oc/pdufa/finreport2004/appendixC.html

Figure 3.1



This section of the paper provides more background information about FDA activities from consultation in preclinical development through review of submitted risk management plans and safety surveillance following new drug approval. At the end of each subsection is a brief summary of current requirements under PDUFA 3.

3.1 Preclinical Development

For truly new therapies, sponsors often request a meeting with FDA to discuss their preclinical findings and review their plans for clinical development. During the preclinical phase of drug development, sponsors' primary goal is to determine whether: 1) the product is reasonably safe for initial use in humans and 2) it is sufficiently effective against a disease target in chemical assay tests or in animal models to justify the cost of commercial development. When a product is identified as a viable candidate, the drug's sponsor then focuses on demonstrating its effectiveness and on collecting the safety data and dosing information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies in humans.

3.2 Clinical Development

The clinical phase of product development (see Figure 3.1) extends from a sponsor's initial submission of the Investigational New Drug Application, to begin testing a new drug in humans (i.e., clinical studies) to submission of a complete NDA)or BLA to FDA for marketing approval.

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies—including sufficient data to permit FDA to assess whether the product and the proposed dose are reasonably safe for initial testing in humans.

- Manufacturing Information—including information on drug composition, stability and manufacturing quality controls, to permit FDA to assess whether the sponsor can adequately produce and supply consistent batches of the drug or biologic for use in the clinical trials.

- Clinical Protocols and Investigator Information—including plans for the design and conduct of the proposed studies in humans.
  - Early-phase clinical studies evaluate the safety and tolerability of increasing doses of the drug, often in healthy volunteers, and proceed from single doses to multiple doses. Later-phase clinical studies involve patients with the disease or condition, and involve progressively larger numbers of people, often treated for longer periods. Clinical protocols may also include parallel studies that focus on special populations, such as the elderly, as well as drug interactions, to determine when dosing adjustments are necessary to ensure drug safety.

  - Information on the qualifications of clinical investigators who will oversee the administration of the experimental compound is needed for FDA to assess whether the investigators are qualified to fulfill their clinical trial duties. In addition, all investigators must make a commitment to obtain informed consent from the research subjects, to have the study reviewed by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the initial IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety and compliance (the toxicology data and the clinical study protocol) to ensure that research subjects will not be subjected to unreasonable risk. When reviewing investigational new drug applications, FDA can decide whether it is reasonably safe for the sponsor to move forward with testing the drug on humans; if FDA concludes trials cannot proceed safely, it puts the IND on clinical hold.

Under PDUFA, FDA's goal is to reply to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of the submission of such sponsor response, and do this for at least 90 percent of such submissions. Rapid resolution of safety issues that led to clinical hold helps ensure patient safety while enabling access to the experimental treatment.

3.2.1 FDA Overs ight and Review of Clinical Trial Protocols During Development

Clinical trials conducted to obtain evidence of the safety and effectiveness of a new drug are described in terms of three successive phases. The table below provides a brief summary.

Summary of Three Phases of Drug Testing		
Phase 1 Number of Patients: 20-100 Length: Several months Purpose: Mainly safety	Phase 2 Number of Patients: Up to several hundred Length: Several months to 2 years Purpose: Dose-response for safety and effectiveness	Phase 3 Number of Patients: Several hundred to several thousand Length: 1-4 years Purpose: Safety, dosage, effectiveness

Phase 1 Studies—begin if FDA does not impose a clinical hold. The focus is primarily on safety, with the goal of determining the relationship between dosing and the patient's systemic drug exposure; the drug's most frequent side effects and whether they are related to dose; and how the drug is metabolized and excreted.

Phase 2 Studies—begin if Phase 1 studies do not reveal unacceptable toxicity. The emphasis is primarily on effectiveness and collection of preliminary data on whether the drug works in people who have a certain disease, and the relationship between dose and effectiveness. For controlled trials, patients

receiving the drug are compared with similar patients receiving a different treatment — usually a placebo or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

Phase 3 Studies—begins if preliminary evidence of effectiveness is shown during phase 2. The goal is to gather more information about safety and effectiveness, about effects on different populations, and about different dosages. Data are also gathered on how the drug interacts when used in combination with other drugs (drug-drug interactions).

Under PDUFA, FDA will evaluate specific questions about the sponsor's special study protocol designs for carcinogenicity, stability and Phase 3 for clinical trials that will form the primary basis of an efficacy claim.

- ***FDA will review scientific and regulatory requirements for which the sponsor seeks agreement.***
- ***FDA's goal is to provide a succinct written response, within 45 days of receipt of the protocol and specific questions, and do this for at least 90 percent of such submissions.***

This FDA review and written feedback ensures safer and more effective study design for participating patients and increases likelihood that resulting marketing application will meet regulatory requirements and gain faster approval.

3.2.2 Sponsor-Requested Meetings With FDA During Clinical Development

Sponsors usually request to meet with FDA during their product's clinical development. The two most common meeting points are at the end of phase 2 clinical trials and just before a new drug application (NDA) or a biologic license application (BLA) is submitted to FDA for marketing review.

End of Phase 2 Meeting—in which sponsors seek FDA input on their Phase 3 clinical studies that are generally pivotal to FDA application review and market approval. Phase 3 studies are designed to demonstrate effectiveness in accordance with FDA written guidance or individually developed (e.g., drug or disease specific) study expectations, the duration of effect, and the populations that will be studied. The studies are also designed to provide adequate assessment of safety, including concerns raised by other members of the drug class or by phase 2 observations.

Pre-NDA/BLA Meeting—in which sponsors seek to discuss what FDA expects to see included in the submitted NDA or BLA application. The discussion between the FDA and the sponsor would generally address concerns raised during clinical studies and the limitations of those studies and planned risk management tools (labeling and others) to address known and potential risks. The discussion will include suggestions for phase 4 studies, if such studies are warranted. In addition, the meeting will consider any proposals for targeted post-approval surveillance, including attempts to quantify background rates of risks of concern and thresholds for actions. The intent of these discussions will be for FDA to get a better understanding of the safety issues associated with the particular drug and any proposed risk management plans, and to provide industry with feedback on these proposals so that they can be developed fully and included in the NDA submission, if needed.

Under PDUFA, FDA's goal is to notify the sponsor in writing, of the date, time, place and FDA participants for a formal meeting within 14 calendar days of the sponsor's request. FDA's goal is to meet the following timeframes for 90 percent of requested meetings:

- ***Scheduling Type A Meetings-- which are necessary for an otherwise stalled drug development program to proceed, -- within 30 calendar days of FDA receipt of the meeting request.***

- ***Scheduling Type B Meetings--pre-IND, end of Phase 1, or end of Phase 2/pre-Phase 3, pre-NDA/BLA meeting — within 60 calendar days of FDA receipt of the meeting request.***

- ***Scheduling Type C Meetings—any other type-- within 75 calendar days of receipt of the meeting request.***

Earlier consultation and feedback from FDA on the sponsor's development program will improve the quality of development including safer and more effective study design for patients and increases the likelihood that resulting marketing application will meet regulatory requirements and gain faster approval.

3.3 FDA Filing and Review of Submitted Marketing Applications (NDA/BLA)

If a sponsor successfully completes the clinical development phase for a new drug, the next step is to submit an NDA or BLA to FDA. Since 1938, every new drug has been the subject of an approved NDA before it could be sold in the United States. An NDA (or BLA) includes all animal and human data and analyses of that data, as well as information about how the drug behaves in the body and how it is manufactured. The data gathered during the animal studies and human clinical trials of an IND application become part of the NDA. Under law, no pertinent data may be omitted.

When an NDA or BLA is submitted, FDA has 60 days to determine whether the application is complete enough to file and be reviewed. The FDA can refuse to file an application that is incomplete (e.g., required studies are missing). Once the application is filed, the review schedule begins, and FDA monitors the progress of the application over time. FDA expects to review and act on at least 90 percent of NDAs for standard drugs and biologics no later than 10 months after the applications were filed. The review goal is 6 months for priority drugs and biologics.[2]

The NDA/BLA submission should provide enough information to permit FDA reviewers to reach the following critical decisions:

- The drug has been shown to be effective for its proposed use or uses.
- Safety has been assessed by all reasonably applicable methods to evaluate safety.
- The drug is safe for its intended use, that is, the benefits of the drug outweigh the risks for the doses being proposed for approval.
- The drug's proposed labeling (package insert) provides adequate directions for use.
- The methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

Once an application is filed, an FDA review team — medical doctors, clinical pharmacologists, chemists, statisticians, microbiologists, pharmacologists and other experts (see box below) — evaluates whether the studies the sponsor submitted show that the drug is effective for its proposed use and has been shown, on the basis of an adequate safety assessment, to have an adverse effect profile that allows a conclusion that the drug is safe for its intended use at the doses proposed by the sponsor. Because no drug is absolutely safe, "safe" in this sense means that the benefits of the drug appear to outweigh its risks.

[2] Applications for drugs similar to those already marketed are designated as "standard," while "priority" applications represent drugs offering significant advances over existing treatments.

Typical FDA Drug Review Team

Chemists focus on how the drug is made and whether the manufacturing process and packaging are adequate to ensure the identity, strength, quality, and purity of the product.

Pharmacologists and toxicologists evaluate the effects of the drug on laboratory animals in short-term and long-term studies.

Physicians evaluate the results of the clinical tests, including the drug's adverse as well as therapeutic effects, and whether the proposed labeling accurately reflects the effects of the drug.

Clinical pharmacologists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized and eliminated.

Statisticians evaluate the designs for each controlled study and the analyses and conclusions for safety and effectiveness based on the study data.

Microbiologists also participate in the review of anti-infective drug products and of products that occur as solutions or as injectables. For new biological products, the microbiologist may also be a product specialist focusing on how the biologic is manufactured and packaged to ensure potency and purity.

The review team analyzes study results and looks for possible problems with the application, such as weaknesses in the study design or analyses, and missing information that may be critical to determining drug safety. Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to make a decision. Just as critical as the assessment of observed side effects is the determination of whether the safety assessment was of adequate scope. Each reviewer prepares a written evaluation containing conclusions and recommendations about the application. These evaluations are then considered by team leaders, division directors, and office directors, depending on the type of application.

In the course of its review, FDA may also call on advisory committees, made up of outside experts who make recommendations to FDA. Whether an advisory committee is called on depends on a number of things; for example, whether a drug raises significant safety questions, whether it is the first in its class, or is the first for a given indication.

If the drug presents a significant documented risk, and sometimes even if the concerns about such risks are theoretical, the NDA submitted by the sponsor may include proposed risk management tools, plans, and protocols for further studies. Both the FDA pre-market review and post-marketing surveillance staff are involved in the review of the risk management plan. When such a plan is needed, the risk management plan will be part of the overall safety and risk-benefit analysis. In some cases, FDA may seek a commitment from the sponsor for the conduct of specific studies after the drug is approved (phase 4 studies).

After a BLA is approved for a biological product, the product may also be subject to official lot release. If the product is subject to official release by FDA, the manufacturer submits samples of each lot of product to FDA. In addition, FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

Under PDUFA, FDA commits to perform a complete application review and will issue an action letter within a specified timeframe. The action letter will either state that the product is approved for marketing, is designated "not approvable, or the product is designated "approvable" if the sponsor can address the deficiencies detailed in the action letter. Sponsors receiving an approvable letter will often try to address the deficiencies and will then resubmit their application.

Under PDUFA FDA's goal is to review all filed original NDA/BLA submissions within the following time frames:

- ***Review and act on 90 percent of priority applications within 6 months.***
- ***Review and act on 90 percent of standard applications within 10 months.***

For all NDA/BLA resubmissions,

- ***Review and act on 90 percent of Class 1 resubmissions within 2 months.***
- ***Review and act on 90 percent of Class 2 resubmissions within 6 months.***

Rapid and complete review of new drug applications ensures rapid access to new medic ines shown to be safe and effective; with priority given to products with greatest public health benefit. It also ensures complete information for sponsors to do the additional work needed to show that their product is safe and effective.

Following approval of an original NDA or BLA, a sponsor may later submit an application to expand the disease indications included in the drug labeling. This application often includes additional clinical study data to support the proposed change in labeling, and is referred to as an Efficacy Supplement. FDA's review of Efficacy Supplements is very similar to the review of original NDAs and BLAs, and results in an action letter to the sponsor outlining FDA's decision.

Under PDUFA FDA's goal is to review all filed original Efficacy Supplements within the following timeframes.

- ***Review and act on 90 percent of priority efficacy supplements within 6 months.***
- ***Review and act on 90 percent of standard efficacy supplements within 10 months.***

Rapid and complete review of new drug applications ensures rapid access to new medicines shown to be safe and effective; with priority given to products with greatest public health benefit. It also ensures complete information for sponsors to do the additional work needed to show that their product is safe and effective.