

PDUFA Lays the Foundation: Launching Into the Era of User Fee Acts

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The Origins of User Fees

From the Food and Drug Administration's (FDA's) perspective, the history of user fees extends back several decades before passage of the first Prescription Drug User Fee Act (PDUFA) legislation in 1992. From the 1950s through the 1980s, the concept of user fees, or "user charges," was being considered across federal agencies, including FDA.

In August 1983, FDA's Office of Planning and Evaluation issued one of the agency's most detailed studies to date assessing the latest proposed government initiative on "user charges" at FDA. This time, the agency addressed new recommendations offered by the Reagan administration's Grace Commission (Private Sector Survey on Cost Control). The report reiterated, as the agency had done for at least the past three decades, FDA's many concerns about the wisdom and feasibility of charging fees to the food, drug, and cosmetic industries for any of its regulatory and review activities. Industry had so adamantly opposed all past user fee proposals that their continuing opposition was assumed for purposes of FDA's 1983 analysis. Less than a decade later, however, with the cooperation of both FDA and the drug industry, President George Bush signed the 1992 Prescription Drug User Fee Act and under the Clinton administration, the first user fees to support drug review activities were collected. PDUFA was a bold initiative, largely experimental, and the endeavor quickly proved transformative in both anticipated and some unanticipated ways as well. Almost two decades later, it has created a new "norm" for drug and biologics reviews by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), and has profoundly affected the rest of FDA as well. None of these changes, however, could have been envisioned in the 1950s when FDA was first asked to consider collecting "user charges" to support some of its "beneficial services" to food and drug manufacturers.

Early Economic Analysis

FDA's first formal rejection of the user fee concept was issued in response to a request from the Bureau of the Budget (BOB) for comments on a draft circular on the subject. Although the U.S. ran a deficit throughout the 1950s, government costs, as a percentage of gross domestic product, were the lowest in the nation's (post-World War II) history.¹ This fiscal austerity spurred the government's interest in user fees. In appropriations hearings preceding passage of the 1952 Independent Offices Appropriation Act (IOAA) (32 U.S.C. 483 a.), the House had expressed concern that the government was providing services to special "beneficiaries" for which it was not being compensated. Incorporated into the IOAA, therefore, signed on August 31, 1951, was the provision referred to as the "User Charge Act."

It is the sense of the Congress that any work, service, publication, report, document, benefit, privilege, authority, use, franchise, license, permit, certificate, registration or similar thing of value

or utility performed, furnished, provided, granted, prepared or issued by a Federal agency ... shall be self-sustaining to the full extent possible.²

When BOB sent its draft circular to FDA, William Goodrich, the Department of Health, Education, and Welfare's (HEW's) Assistant General Counsel for the Food and Drug Division, offered his legal opinion. Goodrich, usually referred to as FDA's Chief Counsel, was one of its longest tenured, most respected, and most successful lawyers. Goodrich argued that such new fees were precluded by fee provisions in the federal Food, Drug, and Cosmetic Act of 1938 (FDCA), which already specified the activities for which fees could be charged: insulin certification, color certification, tea importation, certain kinds of information requests, and for the supervision of articles subject to reconditioning. Such specificity in the FDCA, as Goodrich interpreted the statute, implicitly precluded the imposition of other fees. Goodrich clearly anticipated a legal challenge over the fees by industry. On the operational side, Commissioner Charles Crawford felt that in addition to creating more work for the agency during a severe budget crisis, fees for new drug activities would discourage companies, especially small ones, from filing New Drug Applications (NDAs) at all.³

Again in 1957, the BOB, now under the Eisenhower administration, asked FDA to draft legislative language introducing user fee charges into the agency's operations. HEW Secretary Marion Folsom declined to do so in his response dated June 1958. He cited many concerns, including anticipated difficulties in establishing an equitable fee schedule for the many producers which would be affected; fees would create hardships for small manufacturers; and adversely affect informal government-industry cooperation which was an important asset to FDA. FDA and HEW also argued more fundamentally that they could not even identify "services and benefits" which might accrue to any particular sponsor that might subject it to the proposed fees. The agency's firmly held conviction was that the 1938 Act had been enacted for the protection of the public and the benefit of consumers. Food standards, to cite a single example under the statute, were to be issued expressly "in the interests of consumers." Any benefits which might conceivably accrue to industry or sponsors was deemed secondary to the public health benefits derived from FDA's regulatory activities. NDA reviews, some even argued, provided more benefits to the public than to drug sponsors who they felt would have performed routine drug safety testing even without the government approval process.

Bureau of the Budget's Circular A-25

FDA's objections notwithstanding, BOB issued its guidance document on user fees in 1959. Circular A-25 was written as a guide to help agencies develop a uniform system of charges for government activities perceived to offer benefits to recipients "beyond those accruing" to the public at large. The circular defined as many government "services" as possible, ranging from patents to crop insurance, and safety inspections for aircraft to after-hours meat and poultry inspections. There were three important provisions of the BOB circular, which would frame future user fee debates within FDA and other agencies and eventually for the courts as challenges moved through the system on their way to the Supreme Court.

In contrast to its many examples of appropriate government charges, Circular A-25 listed only a few situations that could create exemptions from charges for government services under the User Charge Act of 1951. The most important of these applied to cases in which the identity of the

ultimate beneficiary was obscure and the service could be primarily considered a benefit accruing to the general public. The circular cited "the licensing of new biological products" as a specific example of an appropriate use of this "public benefit exclusion." FDA felt confident that its operations fell squarely within this exclusion.

Circular A-25 also dictated that the government's user charges be calculated on the basis of "full cost recovery," and not with regard to any assessment of the value of the benefit to the recipient as had been allowed under the original User Fee Act. Fees would be calculated to cover both direct and indirect government costs including salaries, benefits, operating expenses, management and supervisory costs, research, enforcement, and costs related to standards and regulation. All were cited as expenses which could legitimately be covered by user fee assessments. Finally, while acknowledging that Congress might consider changing the policy, Circular A-25 directed that collections go to the Treasury rather than to the agencies responsible for collecting user fees.

While it is unclear whether or not the Circular actually helped create a more robust user fee program within the federal government, that would seem unlikely because the proposed program offered little incentive for individual agencies to comply. All user fee revenues were to be credited to the general Treasury and there were no provisions for new appropriations to cover the costs of assessing and collecting the fees during a decade that was already characterized by fiscal frugality. The BOB, however, soon appreciated the shortcomings of this approach and began to consider more direct actions to encourage recalcitrant agencies such as FDA to collect user fees.

Not until halfway through the Johnson administration was FDA again asked to assess its user charge policies at which time it dutifully reported back through HEW in 1965 that its regulatory activities fell under the public benefit exclusion of Circular A-25. Not to be deterred, the BOB responded with specific examples of programs which it felt should be subject to user charges: food additive approval, inspection of imported foods and drugs, inspections of drug factories and the processing of NDAs. HEW was asked to "promptly develop specifications for legislation" to establish "fair and equitable" charges for these activities. For the first time the BOB is reported to have seriously considered reducing FDA appropriations by the amount it estimated should be collected in the form of user charges - roughly a third of its budget in 1967. This was the first, but by no means the last, instance in which an administration tried to force FDA's hand on the issue by threatening to cut the agency's annual appropriations and forcing it to either make up the shortfall through user fees or lay off skilled personnel. In this instance, HEW Secretary John Gardner, then enjoying the support of President Johnson at the height of Johnson's Great Society initiative, responded more directly and forcefully on behalf of FDA.

These activities are for the benefit of the consumer and should continue to be paid for through general funds derived from our graduated income tax. We should not now switch to a national policy of adopting what amounts to a highly regressive tax on food and drugs.

Companies, they felt, would pass increased costs onto consumers in the form of higher drug prices, in which case the poor and elderly would bear a disproportionate share of the burden.

GAO Endorses User Fees for NDAs

In 1966, the General Accounting Office (GAO) weighed in on the issue through its own communications with HEW. GAO too felt that some user fees, especially those for NDA processing, were appropriate. Again HEW responded in 1967 that any benefits from FDA's drug activities accrued to the public rather than regulated industry. The issue was not raised again until early in the Nixon administration. GAO issued its own report on November 4, 1971, in support of user fees for NDA processing. This time GAO raised the issue with the Senate Appropriations Committee in 1972, and in early 1973 the Office of Management and Budget (OMB, formerly BOB) again requested that HEW prepare a proposal which would extend user fees to agency activities which benefit industry. Although this time HEW did create a draft proposal, it included an analysis of the projected economic impact that user fees would have and concluded that not only would costs be passed along via the normal channels of wholesalers, distributors and retailers, but the increased costs would also be borne by federal, state and private purchasers of FDA regulated products. The HEW analysis projected that costs would exceed the revenue from user fees by a substantial amount. It is not clear how persuasive this argument incorporating economic projections may have been to OMB. The OMB Director at that time was Casper ("Cap") Weinberger, whose own staff dubbed him "Cap the Knife," for his cost-cutting prowess.⁴

It is possible that the economic argument did carry some weight, but his tenure as HEW Secretary was relatively brief (February 1973 to August 1975). More likely is the fact that two Supreme Court rulings issued in 1974 required re-examination of the government's guidelines on the collection of user fees. Regardless, FDA did not have to defend its position on the issue of user fees again until after Ronald Reagan took office in 1981.

By the early 1980s, many government agencies had already dealt with a multitude of user fee related issues both administratively and through the lower courts.⁵ In 1974, however, the Supreme Court had clarified aspects of the user fee programs through challenges to fees in two government agencies, the Federal Power Commission (FPC) and the Community Antenna Television System (CATS).⁶ The court's pronouncements and reasoning had the effect of codifying the provisions of Circular A-25. The high Court agreed that the government had the right to assess user fees so long as there was an "identifiable" recipient of "special benefits" from a government agency or entity. In the absence of such an identifiable beneficiary, however, the public benefit exclusion remained in effect. Government agencies could collect user fees but they could not attempt to collect the total costs of a program or service in cases in which government benefits accrued not only to an identified beneficiary but also to the public at large. The Court also required agencies to distinguish between actual beneficiaries and potential beneficiaries of covered benefits and services. In other words, agencies could not impose blanket assessments on an entire industry, for example, if some companies or recipients received benefits through participation in the program and some did not.

Structuring User Fees

These decisions opened the way for consideration of a multi-tier fee structure for agencies such as FDA, whose "benefits" accrued both to the public and to regulated industry. FDA, for example, would need to divide its total costs for a specific activity into a public health component and an industry benefit component for the purpose of assessing user fees. So long as

fees were carefully itemized and independently assessed, and the specific benefits accruing to identifiable beneficiaries could be correlated and justified, and the agency did not attempt to recoup the full costs of a program, then the Court appeared to consider user fees a legitimate government activity. A system created in accordance with the Court's own guidelines, in fact, would lessen the certitude of litigation.

The Grace Commission Report

In 1981, President Ronald Reagan appointed Arthur Hull Hayes to succeed Donald Kennedy as FDA's Commissioner. In 1982, OMB immediately addressed the issue of FDA user fees in the agency's budget review for 1984, even going so far as to suggest that the new fees could raise funds FDA had originally requested through its appropriations process, to enhance FDA's research program and update its laboratory facilities. This new "dangling carrot" approach presaged reforms soon recommended by the "Grace Commission." In 1982 President Reagan requested a massive study of government waste from an extra-governmental group. This Private Sector Survey on Cost Control (PSCC) was conducted by a group founded by J. Peter Grace, a successful businessman. Funded entirely by private contributions, corporate executives and community leaders directed the work of 2,000 volunteers who combed through federal programs looking for waste. The group was ambitious. Grace himself charged the group to "work like tireless bloodhounds to root out government inefficiency and waste of tax dollars."⁷ The "Grace Commission" Report ultimately occupied 47 volumes and 21,000 pages. The commission recommended important changes in the administration of federal user fees.

The commission's overall intent was to reconfigure the "user charges" system, recasting it to conform more closely to business models. Towards that end, the commission first recommended redefining the term "user charge" to subject all government services with an identifiable recipient to a user fee without regard for any ultimate beneficiary. Second, in stark opposition to the policy established in Circular A-25, the commission recommended that consideration be given to setting prices for services other than on the basis of "full cost recovery" to maximize productivity, cost recovery and program efficiency. In order to utilize market forces and harness them for the government's benefit, prices for services could be based, when deemed appropriate, on the value of the service to the recipient.

Third, recognizing the disincentives which had worked against user fees in the past, a recommendation was made to create positive incentives for participation by directing revenue into "revolving funds" for program operation and exempting user charge activities from full-time equivalent (FTE) ceilings and hiring freezes. Comparable to private sector motivations, the proposal allowed user fee programs to operate outside of the normal government budget constraints which mandated that all appropriated funding be spent by the end of the fiscal year or forfeited. Fees could be carried over from year to year to sustain user fee programs as fee revenues fluctuated. Specialized personnel could be hired when needed and protected from layoffs if program revenues experienced temporary declines. Finally, the commission recognized that an effective user charge program would require changes and upgrades in the accounting and management infrastructures used to support them and recommended authorization for the creation of such specialized programs as might be required.

Although the PSCC Report issued in May 1983 did not specifically recommend that any FDA activities be subjected to user fees, it did offer some new criteria for the agency to consider. For the first time there was mention of the need to consider whether fees might potentially affect economic behaviors such as competition, employment, investment, productivity, innovation or international trade. The report also recommended safeguards to insure that user fee services remain "discrete" from enforcement responsibilities so that the fees would not be misconstrued as an extra-legal fine. Commissioner Hayes agreed to a reassessment of the user fee issue in light of the Grace Commission's recommendations.

FDA Assesses Implementing Fees

FDA's Office of Management and Operations User Charge Study was released in August 1983. The report emphasized that opinions differed on the prospect of user fees within FDA itself. Members of the FDA Policy Board, meeting regularly, had not reached a consensus. The Board, made up of FDA's top management, included all agency Center Directors. Senior leaders in the Center for Devices and Radiological Health (CDRH), for example, felt that its inspections were a legal requirement and therefore not a service to a specific firm. They also felt that forms processing and review activities should be exempt from fees because they did not require positive action: a non-response by the agency within a specified period was tantamount to approval. CDER maintained as it had all along that fees for Investigational New Drugs (INDs) would prove to be a disincentive for innovation. Only 25 percent of INDs, it reported, were from commercial sponsors and 4 out of 5 of them were never commercialized. CDER, however, did feel that inspection activities related to NDA approvals merited closer study.

FDA program analysts examined the potential for assessing user fees for NDAs, INDs, the cosmetic program, food petitions, inspections, new device reviews (NDRs) and radiological product recalls. Exercising due diligence, analysts determined that only two of the activities met all the criteria for assessing user fees: drug and device reviews and food additive petition reviews. These were necessary to meet a legal requirement for approval before a firm could sell products subject to regulation. For the other activities, FDA felt that business received no special benefit. Officials felt inspections were particularly unsuitable to user fee charges since they were not conducted on a regular schedule, and any firm inspected more frequently than its competitors might indeed consider fees paid "per inspection" as discriminatory penalties. The report settled on an in-depth analysis of user fees for new drug reviews. Drug fees were the most obvious choice and potentially, the most lucrative.

Among the more important challenges FDA anticipated was the need to insure that legal requirements were met in setting fair and equitable fees. In the case of NDAs, some means of assessing fees was needed that would differentiate among the myriad activities subsumed under the generic heading of "NDA." Such activities ranged in complexity from approvals of new chemical entities, to that of new dosage forms of an existing drug, a much easier task, and from considerations of a new and important indication for an approved drug, to a minor labeling change. The fee structure would also have to distinguish between new drugs offering greater benefits such as new molecular entities (NME) and "the sixth member" of an established class of drugs. FDA felt the most considered approach would rely on an "average fee structure" created for each kind of NDA. Such a fee system would be complicated to administer. Fees would have

to be waived in the case of orphan drugs and drugs with little commercial potential. Abbreviated New Drug Applications (ANDAs) fell into a grey area since they could be considered a sole benefit to an individual firm because the drug was already on the market, or as a public benefit, since it could make available a much cheaper drug of any acceptable quality. The agency was particularly concerned about fees "complicating our relationship with components of the regulated industry and the research community."⁸

There was also the issue of when to collect fees: upfront for all applications whether they were successful or not, or only for approved NDAs (roughly 70 percent). At one point, the Department of Health and Human Services (HHS) suggested that FDA consider fees for what it deemed to be "nuisance NDAs." The first review would be exempted as a public benefit but fees would be assessed for subsequent reviews. This would encourage sponsors to submit accurate and complete applications. Officials, however, had to admit that FDA itself frequently requested new data. In reality, it was well known to astute observers that new drug sponsors counted on the fact that FDA would not act quickly on their initial submissions and used the delay to fully complete their application before it came up for review.

FDA Rejects Fee Proposition

Having given the user fee issue more sober and detailed study than ever before, FDA officials nonetheless rejected the concept again and returned to their original historical/legal argument: The legislative history of the FDCA clearly showed that the intent of the 1938 statute was to protect consumers. Congress would not have needed to enact a federal food and drug statute if it had not considered the public to be the law's ultimate beneficiary. While premarket approval was required for industries selling regulated products, any commercial benefit from the transaction was deemed slight - in no way equivalent to that conveyed by a patent which grants exclusive marketing rights.⁹ The legislative intent behind the FDCA constituted prima facie evidence that FDA regulatory and review responsibilities fell under the public benefit exclusion of Circular A-25.

The report detailed other reservations about the imposition of user fees on the regulated industry. In addition to concerns about the costs, both direct and indirect, of litigation that was certain to follow, there was also an appearance issue. Would, in fact, FDA's acceptance of funding from regulated industry be perceived as compromising the agency's objectivity? Was there the potential for a true conflict of interest? In the case of a controversial decision, would the public assume that conflict of interest played a role in the decision or decision-making process?

Officials did consider the economic ramifications of user fees, as suggested by the Grace Commission, and worried that fees might change the dynamics of the "NDA marketplace" in unpredictable ways. Revenue projections based on historical norms might be inaccurate and make the program unsustainable if submissions declined. The creation of the "revolving fund" to support the program at the agency level, they warned, "makes the Agency very dependent on the collection of these user charges for its very existence."¹⁰ Regulated industry could also be expected to "exert more influence over the NDA process once they are paying substantially for it." Finally, FDA warned again that the user fee concept ultimately involved issues of social policy: higher drug prices to pay for them would ultimately be paid by those least able to afford

them. The ultimate costs were anticipated to exceed the revenue generated through user fees when all purchasers of new drugs were considered.¹¹

FDA's concerns were indeed problems in search of solutions. So long as both industry and FDA remained dismissive toward the concept of user fees, however, potential stumbling blocks merely buttressed mutual opposition. Later, with larger changes in play, FDA and industry did come to the same table for a serious examination of the benefits and risks which might accrue to each from user fees. In a conciliatory environment, the same specific issues became key issues for negotiation.

Congress Debates User Fees

Many factors invited reconsideration of user fees by regulators, regulated industry, Congress, and the Reagan, Bush, and Clinton administrations during the 1980s and early 1990s. First and foremost was the country's large and growing deficit. Under the Reagan administration, government spending increased and the national debt rose from \$997 billion to \$2.85 trillion by the end of his term of office. Moreover, the U.S. crossed a critical threshold as it lost its status as the world's largest creditor nation and became instead, the world's largest debtor nation.¹² One economist active in the administration recalled that although he was "not nearly as successful as he would have liked, Reagan promoted privatization, contracting out, and user fees at every opportunity." Beginning in 1985, the administration regularly proposed user fees as part of each fiscal year budget for FDA. The plan was for user fees to offset appropriated funds and the savings to the government would be applied against the federal debt.

Looking back, an FDA administrator recalled the intricacies of the game of "appropriations chicken" played annually leading up to PDUFA, involving HHS, the House Appropriations Committee and its Agriculture Subcommittee, and Congress.¹³ HHS would include offsetting user fees in its proposed FDA budget each year. Each year the fees grew substantially larger. By the 1993 budget cycle, the proposed fees would have constituted nearly 25 percent of the agency's total appropriations¹⁴ (\$200 million out of \$971 million). Each year the Democratic Congress and key Congressional Committees refused to approve the fees, citing FDA's primary responsibility to protect the public. Each year Congress voted to restore FDA's funding. Senator Ted Kennedy, in particular, was adamantly opposed to the idea of becoming dependent on user fees, fearing that FDA would end up in industry's pocket. Key opposition to user fees also came from Congressman Jamie Whitten (D-Miss), chairman of the full House Appropriations Committee who led House efforts to block their adoption. Since FDA appropriations are actually paid through the Agricultural Appropriations Act dating back to the 1906 Pure Food and Drugs Act, USDA was repeatedly forced to restore FDA's funding with its own appropriated dollars. This arrangement certainly operated to the benefit of HHS which was not inclined to draw attention to its zero-sum game advantage. While the White House did not concern itself with how FDA got funded, the Agricultural Appropriations Subcommittee, on the other hand, became increasingly frustrated by the gamesmanship over FDA appropriations, and increasingly slow about restoring funding. In the meantime, FDA itself operated in an atmosphere of annual uncertainty. On more than one occasion, funding restoration was so uncertain that letters were sent to FDA employees warning of the possibility of staff layoffs.

In 1985, FDA itself tried to break the impasse on user fees and published a proposed regulation under the User Charge Act which would have imposed user fees for NDAs and ANDAs. Frank Young, FDA Commissioner during this period (1984-1989), recalled in 2007 that FDA's efforts and its early fee proposals "reflected a moment of desperation. No one really wanted to go this route." Industry immediately objected to what it called a "tax on innovation." FDA explained its own abrupt turnabout on the issue of user fees by pointing to unprecedented concerns about the current and likely long-lasting effects of massive government deficits on agency funding.¹⁵ Inadequate funding undermined agency operations overall, and CDER, in particular, was described as "resource poor." The Pharmaceutical Manufacturers Association, however, while opposing FDA's proposed regulation, did hint that it was not closing the door to all fees under all circumstances when it expressed particular concern over the fact that industry's fees would disappear into the black hole of the federal debt rather than benefiting CDER and FDA. Industry, from the very beginning, resisted associating user fees with the federal deficit. Indicative of this opposition was the fact that the term "deficit reduction user fee," which had been in use prior to that time by outside observers such as the Congressional Research Service (CRS), quickly disappeared when serious negotiations began over simply "user fees."

By all accounts, drug sponsors had much to complain about with regard to FDA's new drug review activities both past and present, and even looking into the future. FDA had already come under withering criticism for its perceived role in allowing U.S. drug approvals to lag behind those of other countries. Debates in the media and among academics and even in Congress on this so-called "drug lag" issue gave rise to a growing concern that other countries were reviewing new drugs more quickly, thus making new life-saving drugs available to patients sooner overseas than in the U.S.¹⁶ Current review times did nothing to dispel the notion. Review times for NDAs and ANDAs actually were growing steadily longer. The pharmaceutical industry was increasingly concerned that FDA did not have the resources it would need, not just to evaluate current applications, but to evaluate future new products. Reviewers, for example, would need up-to-date knowledge of advances in such disciplines as advanced biotechnology and genetic research, just to enable them to do their jobs.

The High Cost of New Drug Review

CDER certainly had money problems, but it also had longstanding management problems.¹⁷ As one manager recalled, "[before PDUFA] the drug review process was never considered manageable." As a result, it could take years, for example, for a review division to address an application and then, just as inexplicably, it could be set aside for an unspecified amount of time before being picked up again as one group waited for another to complete its piece of the work. Industry complained about its lack of access to reviewing officials and lack of information about the status of its applications. Meetings with officials would have helped, but they were often considered a privilege because there were not enough resources to support even required meetings.

FDA had its own complaints concerning "ridiculous games" being played with the review process and joked that companies did their "drug development" on the review clock. "In point of fact," according to a former CDER deputy, "we accepted half-baked NDAs that evolved." Industry would submit an application for a drug with two indications, for example, and leave

blank pages to insert the results of "pending" studies. This started the review clock. As it ticked, the results of the original studies would arrive but along with them, new studies supporting two entirely new indications would be added for consideration. There was no consistency in submission or timing on either side. A review division, for example, might issue a "non-approvable" letter for one indication while other indications were still under review elsewhere, which was perceived by industry and some outside observers as a sign that the entire new drug process was more chaotic than calculated. An FDA official recalls that an NDA submitted "helter-skelter" could "easily" drag out the review process for six or seven years.

FDA's identity as a public health agency, the bedrock upon which its opposition to user fees rested, was grounded in a history linked much more closely to frustrating the sale of products peddled by frauds, charlatans and careless companies than fostering the approval of lifesaving pharmaceuticals. FDA had traditionally worked best and most effectively to protect the public when it turned a skeptical eye to all things medical: from patent medicines to radium laced waters; from womb pessaries to condoms; and from copper bracelets to tape worms for weight loss. The first "wonder drug," however, began to change the agency's medical focus. In 1937, FDA was forced to respond to a deadly drug crisis in which sulfanilamide had been dissolved in a poisonous solvent and marketed as an elixir. The deaths of more than 100 people prompted Congress to rewrite the federal food and drug law in 1938 requiring a new premarket safety notification to FDA (during 1938-1962, FDA did not approve NDAs. FDA's successes often came in spite of slack appropriations and without other tokens of governmental esteem. An early inspector recalled that at one point in the early 1950s, when agency funding hit record lows, supervisors required inspectors to turn in used pens before getting new ones. Shared adversity helped create a particular kind of institutional culture that persisted in spite of scientific advances and in the midst of a pharmaceutical revolution. In 1906, drug chemists could not even figure out what was in most proprietary drug products unless a clever investigator had glimpsed the manufacturer's formula. By mid-century, however, agency chemists could identify almost any drug ingredient and subject it to testing both in vitro and in vivo.

The Public Health Impact of "Drug Lag"

Critics, especially those citing the "drug lag," were quick to point to the downside of a regulatory culture steeped in skepticism. When Frances Kelsey was hailed a heroine on the front page of the Washington Post in 1961 for her refusal to approve the drug thalidomide, a major teratogen that caused thousands of cases of phocomelia in Europe and Canada, for marketing in the U.S., she and FDA were credited with directly protecting the health of potentially thousands of babies in the U.S. FDA's new drug authority in 1962 requiring evidence of effectiveness was an explicit result of its prevention of the marketing of thalidomide. Post- thalidomide, it became a truism that FDA was rewarded only when it was cautious ("show me the data") and took whatever time it felt it needed to fully review a new drug. It took a risk only when it said "yes" to a drug which showed safety problems post-market.¹⁸ One result of a culture of caution was the well-publicized "drug lag." The idea that FDA was indifferent to new treatments, however, was always exaggerated, according to those in the drug review division during that era. Complexity alone, including new statistical models and their interpretations, created some inevitable delays and mitigate against overly simplistic portrayals of FDA's new drug review practices post-1962. The summative effects of changes to the new drug review process instituted by the Drug

Amendments of 1962, and upheld by the Supreme Court in 1973, had changed the pharmaceutical industry itself, demanding of it new study and analytic approaches that demanded considerable learning and practice. The effectiveness requirement alone was potent and transformative. FDA, with some outside assistance, weeded out many ineffective drugs and ineffective ingredients through the DESI (Drug Efficacy Study Implementation) and over-the-counter (OTC) drug reviews, both of which paved the way for industry to divert its not insubstantial resources toward new drug development and the creation of a whole host of truly path-breaking new drugs. FDA pipelines were full with new antibiotics, drugs for heart failure, and other new drugs even before the AIDS drugs assumed center stage, but there was a clearly a growing mismatch between advances in pharmaceutical research and declines in FDA review resources.

The AIDS crisis during the 1980s spurred important changes in the new drug review process, vividly demonstrating that the right drug at the right time could make a real difference when people's lives were at stake.¹⁹ HIV brought home the point that delay had its costs and that in diseases such as AIDS, cancer and Alzheimer's, people were willing to take on more risk in search of effective treatment. So many men (and some women) were dying so quickly from AIDS, a truly devastating disease, that the need for speed was obvious and AIDS became, as one official put it, "the poster child for rapid drug development." Protests by angry young gay men carrying tombstones and feigning death in front of FDA headquarters drew attention to the severity of the crisis, but success ultimately depended on regulators who worked creatively and collaboratively with a broad spectrum of scientists, biostatisticians, regulators, industry and members of the gay community to locate, study, and approve a pharmaceutical solution which would stem the epidemic. Success in rapidly approving treatments for AIDS supported a transformative culture stemming from a growing realization that "promoting public health" through faster new drug approvals could be another, and very effective, means of protecting public health.

PDUFA I (1992)

PDUFA participants credit Gerald J. Mossinghoff, President of the Pharmaceutical Manufacturers Association (PMA), with breaking the impasse over user fees. Mossinghoff came to PMA from the Patent Office, which was totally funded from patent application fees. Appreciating that underfunding at FDA was also detrimental to industry, he looked to identify some common ground between the drug industry and FDA which he could use to broker a deal that would benefit both sides. PMA set out four conditions under which it would support a user fee statute: fees had to be additive to FDA baseline appropriations; they had to be dedicated solely to drug and biologics review; the fees had to be reasonable; and the fees must be part of a long-term commitment by FDA and Congress to effect changes in the drugs and biologics review process. (*Editor's note: For a comprehensive overview of the biopharmaceutical industry's perspective on user fees, see Chapter 2.*)

The intricate chain of agreements, hearings, draft legislation and other events linked with final passage of PDUFA have been studied and summarized in great detail elsewhere, but FDA officials spearheading the negotiations emphasize several points which they felt were critical to the ultimate success of the landmark piece of legislation.

First, Senator Ted Kennedy and Representative Henry Waxman came around to view delays in the drug approval process as harmful, citing a new mantra that "good medicines were good for patients." They also came to believe that inadequate funding was contributing to a poor mindset within the drug review ranks. In the end, Kennedy was instrumental in getting the bill cleared through both houses and onto President George H.W. Bush's desk. It was an election year, however, and Bush had campaigned on his infamous "read my lips: no new taxes" pledge which he was often hard-pressed to defend. There was certainly a fine distinction in some minds between user fees and taxes, so the user fee bill sat on his desk until the 30-day signing period had almost elapsed. Bush finally signed PDUFA into law the last day before the election.

Commissioner David Kessler

Commissioner David Kessler's leadership was critical to the creation of the user fee program. It was Kessler who spearheaded meetings with managers at the Patent Office to look at how FDA user fees might be optimally structured. This quickly led to agreement on the basic outline of a tripartite fee structure which provided a more stable revenue stream for FDA. Fees charged solely for application submissions would have left FDA vulnerable to the ebbs and flows of industry submissions and been unaffordable for some in industry. Application fees, therefore, constituted only one-third of total user fee funding. Fees levied against marketed products comprised the second third. This not only created a second stream of revenue but also required industry to buy into a product registration system. FDA was finally able to bring its inventory of products up to date and dump the "garbage" that had been "clogging up" FDA databases. The agency had a much more accurate database on products actually being marketed. The final third of the user fee revenue stream was to come from "facilities" fees with some adjustments to prevent small companies from paying disproportionate fees. "FDA recognized," noted one administrator, "that a company with 1 plant and 3 products was not the same as one with 50 products and 5 plants."



David Kessler, MD, JD; FDA Commissioner who spearheaded FDA negotiations for PDUFA I. (Source: FDA)

A major consideration in persuading industry to endorse user fees was that they would actually save the industry money. The NDA review times were so long, and the cost of an NDA was therefore so large, that if an NDA was approved even one month quicker, it would reduce the cost of the NDA by more than the user fee.

One of the most important set of negotiations surrounding PDUFA, according to FDA participants, centered around industry's insistence on holding FDA accountable for measurable change in the drug review process through timetables and performance-based standards.

Standards and goals were not difficult for negotiators to agree on for year 5 since "everyone at the table had a pretty good idea of what needed to be done by that time." Instead, difficulties arose when PMA wanted FDA to provide detailed interim goals for years 1-4 to them on a tight deadline. FDA, much to the chagrin of industry negotiators, insisted that it simply could not and would not create performance-based goals without conducting "listening sessions" with FDA's own drug review staff.²⁰ The reviewers, in particular, needed to understand that the law would provide much-needed resources on the one hand, but require strict adherence to process and timetables on the other. FDA did resist pressure to hold reviewers accountable, however. "Think about it from the reviewer's perspective," one FDA negotiator told an industry representative wedded to reviewer accountability, "they have to retrain and then work harder and faster on a deadline for no additional pay."

In fact, FDA soon complained to industry that it had hired and trained new reviewers but just at the point at which they were becoming productive - about two years - industry began to "cherry pick our best, doubling their compensation, and hiring them away." In establishing detailed performance goals, FDA wisely set low standards for the early years to take into account the enormous challenges involved in procuring new space, hiring new staff, training them, and providing them with desks and new desktop technology. The first year's performance goal had, in fact, already been met the previous year, but since the subject of FDA's baseline performance pre-PDUFA had never come up, FDA felt justified in setting a low bar for the first year. This proved wise since the first user fees, in fact, were delayed when the Clinton administration had to be briefed on the new law and approve supplemental appropriations to pay for setting up a collections process before FDA could start billing individual firms.

Implementing PDUFA I

The essence of PDUFA, financially, was that companies would pay a fee for each NDA and Biologics License Application (BLA) they submitted. Industry fees were also assessed per establishment and per product with some allowances for small companies. This influx of funds from user fees quickly began to transform both CDER and CBER. Although PDUFA became an important vehicle pushing policy changes in CDER, organizational changes were the most immediate and obvious change. Prior to PDUFA, six or seven divisions reported to one of only two CDER office directors, the only drug officials empowered to sign off on the approval of an NDA. In the wake of PDUFA, FDA created four new offices and six new divisions. The six office directors now had only three divisions reporting to each of them and signatory authority was extended to the office level.²¹

In return for fees, FDA agreed to eliminate its review backlog, review priority applications for new drugs - those demonstrating significant improvement in the treatment, diagnosis or prevention of a disease - in six months and standard non-priority applications in 12 months. It is important to note, however, that these time goals, were for an action, not for an approved application. An "action" could be a determination, in fact, that a drug was "non-approvable." FDA was meticulously conscious of that distinction, seeing it as critical to a credible review process.²²

Extensive management changes were necessary in order to meet these accountability requirements of PDUFA.²³ Key to creating this new culture of accountability within FDA was a growing reliance on newly recruited project managers. The concept was new to FDA, but many of the personnel who became project officers were not new to the agency. The old Compliance Safety Officer (CSO) positions on product review teams in CDER and CBER were transformed into project manager positions and reviewers had to accept them in their new roles as Consumer Safety Officers. This was not an easy cultural transformation. CSOs were frequently the unsung heroes on most review teams, but reviewers themselves were reportedly often more accustomed to seeing them in a "secretary-like role, schlepping documents to and from the records rooms." Their new duties, however, gave them considerably more visibility and an increasingly important role to fulfill. According to one relieved manager, "the CSOs really grew into their jobs - this was going to be their future and they owned it." They managed PDUFA requirements through tracking systems for budgets, projects and performance, and their work was key in helping to insure that the original PDUFA goals were met as the first PDUFA sunset, and renewal renegotiations had to be initiated.

The PDUFA agreement was based on the concept of a complete application at the time of submission, a complete review by FDA within a defined timeframe, and a complete response. Accountability under PDUFA also depended upon tightened NDA submission requirements. Sponsors had to file complete NDAs and FDA, for its part, was required to issue a complete list of deficiencies and could not dole them out piecemeal. Greater resources facilitated more frequent meetings between sponsors and regulators to streamline the review process beginning in the IND phase.

Finally, there were the improvements that accrued to the entire organization when money was invested in information technology (IT), which was life-altering for most people at FDA - reviewers and non-reviewers alike. A former CDER deputy director recalled that, when he came to the agency in 1989, his office had 66 people and two Wang computers. Desktop computers "brought FDA up to the twentieth century" and increased productivity at its most basic level, the individual drug reviewer's desk. One witness to the changes arising from user fee funding quipped, only slightly tongue-in-cheek, that computers were largely responsible for eliminating the drug lag. The fact that computers eliminated the need for specialized typists to make corrections to hundred-page drug approval documents through six layers of onionskin and retype that same hundred-page document when more extensive changes were needed, went a long way in boosting overall productivity and evening the technology-based playing field between FDA and industry.²⁴

PDUFA II (1997-2002)/FDAMA

By 1997, when the law's sunset provisions came into play, PDUFA was subject to re-negotiation prior to renewal. It was apparent from the beginning that there was widespread support from virtually all sides to reauthorize new PDUFA legislation.

Statistics spoke of the programmatic successes achieved from 1992 to 1997. Median time to approval for standard NDAs was 27 months in 1993. In 1995, total approval time had dropped to 17.8 months. In 1997, when PDUFA was up for re-negotiation, standard approval times had

dropped to 14.8 months. Similarly, median review times for priority NDAs/BLAs had dropped from 13.2 months in 1995 to 9.5 in 2007. Such impressive gains in efficiency and effectiveness were achieved primarily by instituting a managed review process, something that had not existed prior to PDUFA, as well as doubling the size of the review staff.²⁵

PDUFA III (2002)

Successes under the PDUFA program continued to be documented statistically. The success of the original PDUFA and PDUFA II seemed to be magnified and to some extent validated by several revolutionary new drugs that received extensive press coverage during the re-negotiation period for PDUFA III. Two cancer drugs, in particular, were widely hailed as game changers for some patients with cancer and both had been approved within a four-month time frame. Gleevec was the first of these drugs. Safety trials for Gleevec began in 1998, but researchers saw that, as they increased the dose to study drug tolerance, there were dramatic results in patients who were not responding to other treatments. In 1999, preliminary results from stepped-up effectiveness trials also showed dramatic results deemed to be unusual in early trials of a new drug. Gleevec received priority review and in May 2001 it received FDA approval for the treatment of chronic myeloid leukemia (CML), a cancer of white blood cells. Featured on the cover of Time, Gleevec was hailed as the "magic bullet to cure cancer." In 2002 it was approved for the treatment of a rare form of stomach cancer. NIH was more restrained but no less admiring when it explained that the drug "represents a new class of cancer drugs and a new way of thinking about cancer." By targeting abnormal proteins in the cancer cells themselves, Gleevec killed the cancer cell without killing adjacent healthy cells, thus maximizing effectiveness and minimizing side effects. Gleevec was credited with converting a fatal cancer into a manageable chronic disease. The second widely publicized cancer drug was Velcade. Although not formally approved until May 2003, after PDUFA III was enacted, the drug's striking effectiveness in clinical trials for multiple myeloma was known as early as 2000 when one of the first volunteers for an early drug trial achieved a complete and lasting response to the drug, a remarkable result for a cancer patient.

PDUFA II was passed as part of the FDA Modernization Act in 1997. Again, industry was assessed per NDA/BLA, per establishment, and per product. Review times were tightened for standard reviews from 12 months under PDUFA I to 10 months under PDUFA II. Process goals were also established under PDUFA II to facilitate clinical development through greater communication with drug sponsors at various points along the clinical trial continuum. FDA committed to reviewing responses to clinical holds for IND applications within 30 days; holding meetings with sponsors within 30, 60 and 90 days after requests; responding to clinical holds within 30 days; and evaluating special protocol designs at the request of the drug sponsor within 45 days. Finally, IT resources were committed to making electronic submissions possible by 2002.

Despite such evident success, however, FDA's drug review activities were under stress by the end of PDUFA II.²⁶ Financially, the program was on increasingly precarious ground. Previous PDUFA funding estimates had been predicated on projected increases in fee-paying applications of 7 percent per year. Collections were well below that when negotiations for PDUFA III began and deficit spending had left no carryover funds to sustain the program if reauthorization was not

prompt. FDA was finding it more difficult to meet the shorter time frames; reviewers were finding it more difficult to provide early feedback to sponsors and resolve issues earlier in the review cycle; FDA reviewers were foregoing needed training and professional development to meet strict timelines; and FDA staff complained of inadequate time to develop guidance and standards for industry's long-term use and benefit.

Not only had FDA's workload under PDUFA II continued to increase, but Congress had added to the agency's drug-related workload under the larger Modernization Act, with new requirements related to grants of pediatric exclusivity, increased emphasis on international harmonization efforts, and the inclusion of accelerated approval regulations, as well as several other new initiatives. Congress, however, did not add any appropriated dollars to support the modernization law's new requirements. Government appropriations, in fact, had remained at 1997 levels since enactment of PDUFA II. "Timely reauthorization of PDUFA," FDA officials said in 2001, "is one of FDA's top legislative priorities." It was no less a priority for the drug industry, however, which had reaped tangible benefits from PDUFA I and II. Industry, however, had long recognized the need for increased appropriations for FDA. Given that PDUFA had opened the agency to criticism that it was too reliant on industry fees, industry supported and lobbied for increased FDA appropriations in addition to supporting the continuation of PDUFA.

Post-Market Enforcement Obstacles

The withdrawal of several high-profile drugs during the period covered by PDUFA II had drawn attention to the need to identify and manage risks that were identified post-market in an accelerated approval process. In 1997, FDA had recommended the withdrawal of the antihistamine Seldane from the market. First marketed in 1985, it was the first non-sedating antihistamine for the treatment of allergies and a very popular drug. Problems were identified, however, and eventually it carried a boxed warning, but it was not withdrawn from the market entirely until a replacement drug with similar efficacy but without the safety concern had been approved. Although the original approval had not taken place under PDUFA, the popularity of the drug alone drew enhanced attention to the withdrawal.

The demise of Seldane had been quickly followed in June of 1998 with the abrupt withdrawal of Posicor, a drug used to treat hypertension. The drug had been on the market less than a year when reports of dangerous and some fatal interactions with at least 25 other drugs, including antibiotics and antihistamines, surfaced. Taken by nearly a quarter million patients, its withdrawal was described as a "logistical nightmare" for cardiologists faced with notifying patients and switching them to the effective alternative treatments. Publicity about Posicor initiated inevitable questions as to whether the FDA had been hasty in its initial approval under PDUFA, which was often portrayed as a politically "speeded up" drug approval process. Finally, Propulsid, a gastrointestinal drug, had been withdrawn from the U.S. market in July 2000, after reports linked the drug to an increased risk of heart arrhythmia.

The immediate postmarketing period for an approved new drug is always considered somewhat precarious as the drug moves away from study in a relatively small population to prescription distribution in a larger and more diverse population. Postmarketing problems, therefore, are not unanticipated, but there were concerns leading into PDUFA III that the kind of widespread

problems discovered with Posicor after less than a year on the market could and should have been better identified and characterized premarket, even though some had been discussed at an FDA Advisory Committee meeting prior to approval. Faster approval times, which are generally considered to be in the patients' best interest, nonetheless generated a concomitant need to better manage post market risks.

While it was clear that FDA postmarketing activities needed additional funding, there was also debate as to whether such support should come from general appropriations or from user fee revenues. This debate was part and parcel of a larger discussion over the general scope of PDUFA III and whether it would be used, as PDUFA II had been, as a "Christmas tree" for broader drug reform. Ultimately Congress did enact PDUFA III as part of the Public Health Security and Bioterrorism Preparedness and Response Act, but left it relatively "clean," maintaining core PDUFA features while expanding the scope of the user fee program significantly by authorizing, for the first time, the use of fees for certain postmarket risk management activities.



Rose Garden ceremony marking President George W. Bush's signing of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which included PDUFA III, on June 12, 2002. The ceremony, attended by Senate cosponsors Bill Frist (R-TN) and Ted Kennedy (D-MA) and House cosponsors W.J. "Billy" Tauzin (R-LA) and John Dingell (D-MI), highlighted the bipartisan Congressional support for this far-reaching legislation. (Source: James Martin Center for Nonproliferation Studies.)

The primary focus of PDUFA III remained the restoration of the program on a sound financial footing by fully covering review costs moving forward while eliminating the deficit spending. Meeting revenue goals of just over \$1.25 billion between 2003 and 2007 ultimately required that application fees be nearly tripled from \$309,000 in 2001 to almost \$900,000 in 2007. Likewise, overall user fee revenue nearly doubled during that same time period from \$133 million in 2001, to \$259 million in 2007.²⁷

Other priorities during the negotiations centered on balancing performance obligations and resource expectations in order to relieve stress on the program. Enhanced agency/industry relations were achieved by some give-and-take on both sides. Providing time for reviewer training, for the preparation of guidance documents, and for other "off-timetable" activities were agency priorities, while creating measurable timetables to guide meetings with sponsors to

enhance agency/industry interactions was an industry priority. Both were addressed in PDUFA III as was the creation of an enhanced risk management system for newly approved drugs. The provisions of PDUFA III allowed user fee funding for postmarketing initiatives, and authorized payment for certain drug safety activities for up to two years after a drug product was approved and up to three years for those drugs with special risk management requirements.

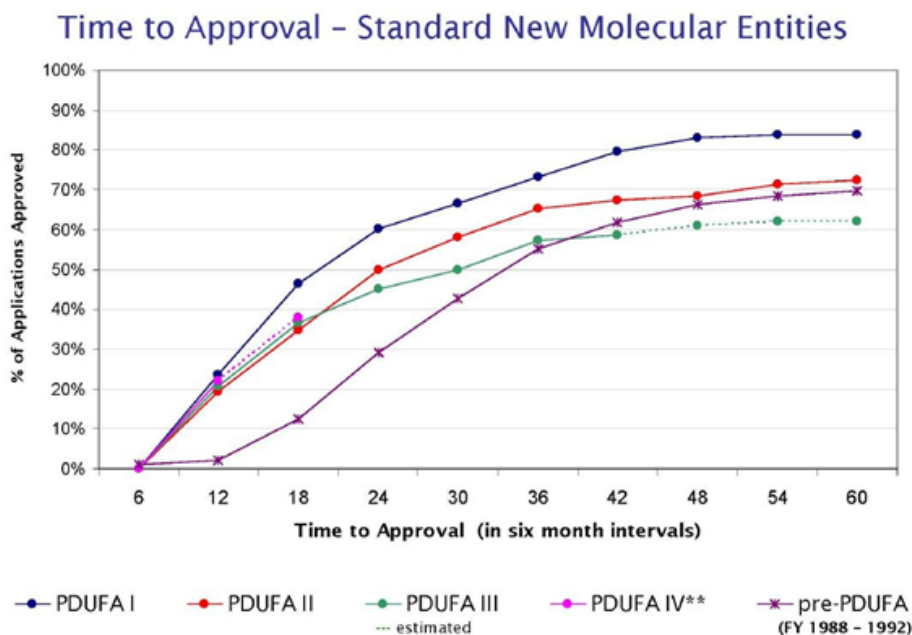
A New Perspective on the PDUFA Sunset

FDA negotiators, by this time, had come to view the law's sunset clause in a positive way, recognizing that it gave all parties time to assess the state of the user fee program between negotiations using explicit evaluation criteria. The opportunity to revisit the program every few years, they felt, strengthened the program by giving each side the opportunity to take account of the previous PDUFA program successes and failures. That said, they were continually confronted with what they considered overly ambitious goals during PDUFA negotiations. What they regarded as overreaching came as often from Congress as from industry. One FDA negotiator recalls wondering how the agency would be able to simultaneously fulfill the new postmarketing safety responsibilities set by Congress under PDUFA III (given some aggressive timelines) and meet the review performance goals in the FDA/industry agreement.

FDA negotiators were of one mind on several other points as well. First, they kept in mind, as one negotiator during PDUFA III put it, that "our job is to negotiate for the public—we work for them." Second, they insisted that industry present a single "industry" perspective. Increasingly, for example, this required traditional pharmaceutical firms and biotechnology companies to achieve greater harmony in order to present their priorities and have them addressed during PDUFA negotiations. Third, FDA negotiators worked hard to address industry needs in a practical and measurable way. User fees were viewed as "process fees," and FDA negotiators ensured that they were used to provide solutions that benefited industry. (Had they not, the monies collected would have been designated an unauthorized tax).²⁸ In PDUFA III, for example, negotiators agreed to a provision that allowed FDA to engage independent consultants to participate in reviews of biotechnology applications. The program was never used, however, and it was dropped from the program in PDUFA IV.

By the end of PDUFA III, it was evident the extent to which PDUFA had shifted resources away from other FDA activities, including research, inspections, training, and other programs in order to meet the agency's commitment to timely drug reviews. In fiscal year 2006, user fees made up 42.5 percent of FDA's total human drug program budget of \$521 million and more than half of the funds dedicated specifically to drug review. The rest came from appropriations that largely supported agency salaries. A Government Accountability Office (GAO) report concluded that PDUFA was responsible for a "rather dramatic redistribution of personnel" within the agency as FDA let staff positions in non-PDUFA domains go unfilled in order to meet PDUFA obligations. Again, chronic resource shortfalls affected all of FDA even in the midst of what appeared to be an effective drug review program.²⁹ Frustration mounted, not just at FDA, but among a large proportion of agency stakeholders as well. A bipartisan alliance of more than 180 FDA stakeholders in diverse fields and with multiple areas of expertise came together in 2006, forming the "Alliance for a Stronger FDA," an organization whose sole purpose was to work for increased agency appropriations. Even the Institute of Medicine (IOM) at this time was quoted as

saying that "an agency whose crucial mission is to protect and advance the public health should not have to go begging for resources to do its job."



The graph illustrates the approval profile of new molecular entities (NME's) approved pre-PDUFA and under PDUFA I, PDUFA II, PDUFA III, and PDUFA IV. Before the original PDUFA was enacted in 1992, 60% of new molecular entities (NME's) were approved within a 60 month period. Under PDUFA IV, review times had dropped significantly and 85% of NME's were approved in the same 60 month timeframe. (Source: FDA, December 2010).

PDUFA IV

There was clearly support for Congressional reauthorization for the fourth iteration of PDUFA in some corners, but there was a new pushback from other corners as chronic and growing appropriations shortfalls showed signs of straining relations within FDA and among stakeholders. At one point, an FDA Commissioner was offered what seemed to many like an excellent idea for a new initiative in an open staff meeting but uncharacteristically cut off the employee, snapping that he was "just trying to keep the lights on." The Bloomberg Press reported that FDA's "addiction" to user fees had come under attack in 2007, and many agreed with that characterization. Lingering unease about the potentially corrupting effects of industry funding on the drug review process and public health protection which dated back to the earliest user fee proposals resurfaced, followed by recommendations for a return to the days of full government funding for drug review activities.

At a workshop in which many former FDA Commissioners participated, held at the George Washington University's School of Public Health in February 2007, former Commissioner Frank Young (1984-1989) reminded his audience that the original PDUFA proposal under his watch had been born of fiscal desperation and concluded that in the years since, "Congress has let the agency down" by imposing requirements without ensuring adequate funding. Young went on to

poll his panel of former commissioners asking them whether or not, "given a choice of having PDUFA or an appropriation of equal amount, which would you take?" They all agreed that appropriations would be preferable. "Appropriations, no question" replied David Kessler, whose tenure spanned the first PDUFA (1990-1997).³⁰

An open letter to Congress in support of PDUFA by several prominent consumer groups contained a trojan horse: the petitioners fully supported PDUFA renewal, but for only as long as it would take to reform the drug approval system and return it to appropriated funding. Another open letter calling for full FDA funding through federal appropriations was signed by 22 drug safety and efficacy experts in March 2007, including former editors-in-chief of the *New England Journal of Medicine*, four members of the IOM drug safety committee, and six former senior HHS and FDA officials. In the meantime, controversies surrounding several drugs and drug classes for which serious postmarket safety problems had been raised brought new questions about the effectiveness of FDA's postmarketing surveillance program. Reviewers at FDA claimed that their warnings about unsafe drugs had gone unheeded while the IOM cited "serious resource constraints that weaken the quality and quantity of the science that is brought to bear on drug safety." In the case of the COX-2 class of non-steroidal anti-inflammatory (NSAID) drugs, serious heart-related problems were identified in follow-up studies. The most prominent name brand COX-2 inhibitors were Vioxx and Celebrex, both of which were easily recognized by consumers who had witnessed television and print advertising for the new drugs.

New Drug Safety Concerns

Reports calling into question the safety of selective serotonin re-uptake inhibitors (SSRIs), including Prozac, as a treatment for depression were particularly disturbing to the public. Taken by millions of patients, sometimes for extended periods of time, SSRIs as a class were found in studies commissioned by FDA to be associated with an increased risk of suicidal tendencies or behavior in children and adolescents with depression. Finally, controversy over the approval process for the antibiotic Ketek led to allegations by FDA staffers who publicly complained that their concerns over the drug's safety were ignored, that the risks of Ketek clearly outweighed its limited benefits, and that it should never have been approved in the first place. Meanwhile, a key clinical trial researcher studying the drug went to prison after pleading guilty to charges of fraud after attempting to cover up evidence of liver problems and liver failure in her clinical trial patients.

Such highly publicized drug safety problems led to new proposals to enhance drug safety in the PDUFA IV negotiations. Meanwhile, proposals to finance FDA through federal revenues rather than industry fees had predictably gone nowhere and like its PDUFA predecessor, PDUFA IV also assumed an overriding duty to ensure that the FDA's drug review program received adequate funding. Base target revenues were increased to \$392 million, up \$87.4 million from PDUFA III. However, PDUFA IV did strengthen pre-market processes by clarifying data requirements needed to support claims, as well as establishing timetables and schedules for discussing product labeling and postmarket follow-up. Provisions were also made to support greater postmarket drug surveillance, including providing funding to strengthen FDA's IT infrastructure in support of enhanced drug monitoring measures. PDUFA IV was reauthorized as part of the landmark FDA statute, the Food and Drug Administration Amendments Act

(FDAAA) enacted in September 2007, which also reauthorized and expanded the Medical Device User Fee and Modernization Act (MDUFMA). The broadest changes came in Title IX, "Enhanced Authorities Regarding Postmarket Safety of Drugs." Title IX granted FDA authority to mandate postmarket studies, clinical trials, labeling changes, and risk evaluation and mitigation strategies (REMS). If FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks, the product may not be marketed without the adoption and implementation of such a strategy. Even if a REMS was not initially required at the time of approval, FDA can require that one be implemented on the basis of new safety information.

One program that appeared particularly amenable to the user fee model during PDUFA IV negotiations was premarket review of direct-to-consumer (DTC) drug advertising. There was general agreement that premarket review of DTC advertisements was an under-resourced area and bringing it under the purview of PDUFA was considered an "innovative idea." However novel, the prerequisite appropriated funds for the program's implementation never materialized, so user fees could not be dedicated to it.

Obstacles to Implementing PDUFA IV

Informed observers believe that PDUFA IV has taken somewhat of a back seat to other FDAAA Congressional mandates carrying 180-day deadlines and other mandatory requirements. FDA's implementation of some PDUFA provisions was hampered when the HHS Secretary took away FDA's direct hiring authority. In other situations it has been difficult to find qualified employees. As a hiring expert explained to one negotiator, "Not many people in the whole country could do this—there are not enough American biostatisticians, and the government cannot match industry salaries."

Once new staff were hired, however, there were problems meeting some performance goals and timelines. A shortage of mid-level managers required senior officials to divert time from their regular work for staff training and mentoring. Additionally, implementation of the many drug-related FDAAA provisions required substantial resources. FDA has been concerned that expectations were not realistic in areas such as REMS implementation strategies and enhanced conflict of interest reviews. Some FDA officials believed that some within Congress did not realize the difficulty involved in meeting a number of the aggressive timelines attached to the FDAAA provisions, with the resources available.

Increasingly there are concerns about the future of user fee payments by the drug industry. For example, with 70 to 75 percent of all prescriptions written for generics, some argue, should brand name drugs continue to pay huge fees while generics pay nothing at all? And even if there were a way to introduce generic drug user fees, which FDA is attempting to do, care would have to be taken to make sure it did not take the form of anything resembling a tax. More broadly, in the context of a challenging federal budget climate and patient and consumer groups questioning the influence of user fees on FDA's integrity, stakeholders will need to consider what mix of appropriations and user fees is ideal for drug review. Such issues and concerns will form the context of future user fee negotiations, as they have for the negotiation of PDUFA V, begun in 2010.

Conclusion

Overall, the PDUFA program has fulfilled the original objective of providing FDA with additional resources in order to conduct more timely premarket application reviews for drugs and biological products. U.S. patients have prompt access to important new drugs, and the pharmaceutical industry can expect a predictable review process. Therefore, PDUFA is a successful program.

However, this success has come with certain costs. As discussed above, these consequences were discernable in the decades-long debate that preceded the enactment of the program. The provision of industry fees to FDA has undermined public trust in the agency, which is perceived by some as having lost independence and credibility as a result of accepting industry money. Additionally, each time a new postapproval drug safety issue is identified, various commentators blame the problem on shortened review times. Such causality is difficult to either prove or refute, and thus the controversy continues. It is possible that better management of these predictable but unintended consequences could have mitigated the reputational impacts on drug regulation.

Meanwhile, the dilemma that began PDUFA—the mismatch between agency funding and its myriad responsibilities—has persisted or worsened in many non-PDUFA funded areas. Appropriators and possibly many administration officials over the years have felt that U.S. drug regulation was adequately provided for by PDUFA, and have directed scarce appropriated resources elsewhere. However, as discussed at the beginning of this account, the one drug program consistently cited by FDA over the decades as under-resourced—its surveillance of drug manufacturing and drug imports—continues to struggle, as numerous Congressional hearings over the past several decades have highlighted. The movement of drug manufacturing outside the U.S. has put much additional stress on FDA's ability to adequately monitor drug facilities and meet the review performance goals in the FDA/industry agreement. These problems are unlikely to be addressed in the context of PDUFA. It is likely the success of PDUFA can be attributed to its focus on a narrowly defined set of problems, with both resources and performance metrics directed at solving these problems. As such, it is worth studying as a successful public-private initiative to address a longstanding problem.

Note: This paper was originally published as "Launching into the Era of User Fee Acts: PDUFA Lays the Foundation" in *PDUFA and the Expansion of FDA User Fees: Lessons from Negotiators*, Nancy Bradish Myers and Anne Petruska McNickle, eds. (Washington DC: Food and Drug Law Institute, 2011), pp. 1-26. Changes have been made to the original published version, and future updates will appear online.

Note on Sources: Original PDUFA files are being processed for accession into RG 88, Records of the U.S. Food and Drug Administration, at the National Archives. All sources for this article will be maintained in the interim at the FDA History Office, Silver Spring, Maryland. We expect that observers and participants in the PDUFA process may have additions and corrections for this article. Please submit them to Suzanne.Junod@fda.hhs.gov.

Endnotes

1. Government spending as a percent of GDP was - 0.39 during the 1950s. U.S. Government 2009. "Historical Tables - Budget of the United States Government, Fiscal Year, 2009.
2. 65 Stat. 290, 31 U.S.C. Â§ 483 a.
3. FDA Annual Reports 1950- 1974 , Department of Health, Education and Welfare, GPO, p. 118. FDA experienced its only reduction in force (RIF) during this period. Politics played a role in the loss of 10 percent of the agency's budget in the 1953 budget cycle. FDA blamed the wrath of a Congressman over the definition of a "baby beet" for the loss. For a more skeptical interpretation, see JAMES S. TURNER, *THE CHEMICAL FEAST* (1970) at 202-204.
4. http://en.wikipedia.org/wiki/Casper_Weinberger (last visited Feb. 17, 2011).
5. C. Gillette & T. Hopkins, *Federal User Fees: A Legal and Economic Analysis*, 67 B. U. L. REV. 795 (1987).
6. *National Cable Television Assn., Inc. v. United States*, 415 U.S. 336 (1974), *FPC v. New England Power Co.*, 415 U.S. 345 (1974).
7. <http://www.reagan.utexas.edu/archives/speeches/1982/31082d.htm> (last visited Feb. 17, 2011). The Grace Commission's successor organization, Citizens Against Government Waste, says that the "report detailed information about the tremendous amounts of taxpayer money literally thrown away by the federal government on mind-numbingly useless and inappropriate spending projects."
8. Commissioner Hayes was particularly concerned about charging for investigational new drug exemptions, which represented about half of FDA's total drug approval resources at the time. "Such charges," he noted, "could discourage some of the very things we have been working hard to promote, such as being certain researchers submit requests for investigational new drug exemptions whenever unapproved drugs are used in their research." Commissioner Arthur Hull Hayes to Assistant Secretary for Health, "User Charges for FDA Regulatory Activities," July 29, 1983.
9. Economic theorists, the agency pointed out, frequently cite FDA regulations as an example of a "public good." As one academic put it, the benefit of food and drug regulation is such that their benefits "cannot be withheld from any individuals." J.H. DUE & A.F. FRIEDLANDER, *GOVERNMENT FINANCE: ECONOMICS OF THE PUBLIC SECTOR* (1969) at 40. Cited in FDA User Charge Study, August 1983 at 40. Copy in FDA History Office, Silver Spring, Maryland. Dr. Robert Temple, CDER's Deputy Director for Clinical Science, (also Acting Director of the Office of Drug Evaluation I (ODE-I) disputes the idea that a drug approval is not the equivalent of a patent, pointing out that the commercial benefit of a new drug approval is actually very comparable to a patent. A patent, moreover, gets a company "nothing at all" until it is granted.
10. FDA User Charge Study, August 1983 at 49.
11. D. SAVOIE, *THATCHER, REAGAN, MULRONEY: IN SEARCH OF NEW BUREAUCRACY* (1994) at 215. FDA User Charge Study, August 1983 at 49.
12. Historical Debt Outstanding, U.S. Treasury Department, http://www.treasurydirect.gov/govt/reports/pd/histdebt/histdebt_histo4.htm (last visited Feb. 17, 2011). Reagan Policies Gave Green Light to Red Ink, WASH. POST, June 9, 2004, available at <http://www.washingtonpost.com/wp-dyn/articles/A26402-2004Jun8.html>.
13. Oral Interview with Mary Jo Veverka, former Deputy Commissioner of Management and Systems, and Mary Pendergast, former Principal Deputy Commissioner. Both served under Commissioner David Kessler (Jan. 10, 2011).
14. B. Kuhlik, *Industry Funding of Improvements in the FDA's New Drug Approval Process: The Prescription Drug User Fee Act of 1992*, 47 *FOOD & DRUG L. J.* 486, n27 (1992).
15. *Ibid.*, at 486, n20. *Agriculture, Rural Development, and Related Agencies Appropriations for 1986: Hearings Before a Subcommittee of the House Committee on Appropriations, 99th Cong., 1st Sess., pt. 3 at 602.*
16. FDA drug officials thought that some of the concerns over the "drug lag" issue were overblown.
17. CDER Deputy Director, Gerald Meyer, remarked that "We do a very good job of making decisions, but we don't make them in a timely manner. We draw a lot of heat for that." "Can David Kessler Revive the FDA?" *Science* 252 (April 12, 1991), p. 201.
18. Critics have failed to pay enough attention to the fact that Frances Kelsey's very presence at FDA signaled the arrival of a new generation of science professionals, including women, at FDA. The first oral contraceptive, Enovid, was approved only six months before her arrival at FDA. The drug reviewer assigned to the NDA, while not unqualified, was a part-time reviewer sent by FDA to medical school for ob-gyn training. Frances Kelsey, in contrast, was a fully credentialed research scientist who, coincidentally, had actually worked on the Elixir Sulfanilamide crisis as a graduate student in 1937.
19. In 1976, the Medical Device Amendment explicitly stated that FDA was to promote the development of medical devices and so FDA had already begun to explore ways of encouraging innovation as a means of

addressing public health needs. This included suggestions to consider classifying new drugs according to their therapeutic potential so that they could be put on a "fast track" to approval. These discussions had begun before the AIDS crisis. Commissioner Donald Kennedy and Deputy Commissioner Sherwin Gardner to FDA Policy Board, "The Peaceful Coexistence of Innovation and Regulation," June 29, 1979. FDA History Office.

20. Robert Temple is credited by observers with bringing the FDA Medical Review Officers into the PDUFA process.
21. Oral interview with Dr. Janet Woodcock, Director, CDER (Jan.,5, 2011).
22. Edits and corrections, Dr. Robert Temple, Feb. 28, 2011.
23. Oral interview with Dr. Murray Lumpkin, former Deputy Director, CDER (Jan. 6, 011).
24. In 1996, during PDUFA II negotiations, PhRMA and FDA began to explore harnessing the powers of the Internet to facilitate information-sharing, forming a separate task force to explore the issue. Gerald J. Mossinghoff, President, Pharmaceutical Research and Manufacturers of America, to Commissioner David A. Kessler, M.D., July 9, 1996. FDA History Office.
25. See, David. A. Kessler, Remarks by the Commissioner of Food and Drugs, FOOD DRUG COSM. L. J. 52:1 (1997).
John Jenkins, e-mail correspondence, 5/23/12, FDA History Office.
26. According to Frank Claunts, Mike Friedman, Acting Commissioner, insisted on negotiating for PDUFA II himself and he felt that he was "too quick to make agreements with industry," which left FDA without the money to sustain performance under PDUFA II. Subsequent PDUFA negotiations were negotiated at the staff level and taken to the commissioner and senior staff for approval allowing some time for internal reflection and debate. FDA Oral History Interview with Franks Claunts, December 8, 2006, pp. 31-32. National Library of Medicine, Bethesda, MD.
27. Initially appropriation increases under PDUFA were calculated based on increases in the Consumer Price Index, but the costs of sustaining the program far exceeded CPI benchmarks. Frank Claunts estimated that staffing costs alone rose an average of 5.9% each year between 1996 and 2006. Oral History, Frank Claunts, p. 35.
28. Oral interview, Theresa Mullin, lead PDUFA negotiator (Nov. 30, 2011).
29. For more on the impact of PDUFA triggers on the rest of FDA, see also Oral History, Frank Claunts, p.
30. Rapid Public Health Policy Response Project, "Reauthorizing the Prescription Drug User Fee Act: How are PDUFA, the FDA Budget, and Drug Safety Related," April 2007 at 5.