

STAKES ARE HIGH IN DRUG AND DEVICE USER FEE TUG-OF-WAR

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Nearly 20 percent of the Food and Drug Administration's (FDA's) operating budget in fiscal 2006 of approximately \$1.9 billion was funded by the drug and medical device industries through three existing user fee programs. Those programs include: Prescription Drug User Fees, Medical Device User Fees, and Animal Drug User Fees. FDA's philosophically disparate constituencies assemble every five years to reauthorize these user fee programs. In the process, they work with the agency and the Congress to extract additional concessions in exchange for the hundreds of millions of dollars paid annually for prompt application reviews.

This "tug-of-war" frequently includes the agency's own request to use these funds for a broader range of administrative functions. In the past, these functions included: improved electronic infrastructure, consolidated workspace, and postmarket surveillance of product safety problems. The "ropes" have again been extended and a new contest has begun. The stakes have never been higher.

User Fee Structure

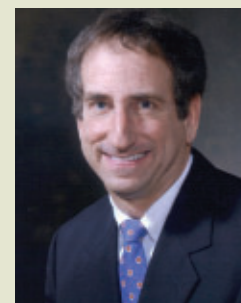
Prescription Drug User Fee Act Fees used to pay the salaries of new drug reviewers at FDA have traditionally

taken the form of application fees, establishment fees and product fees. In Fiscal Year 2007 (Oct. 1, 2006-Sept. 31, 2007), the fees from a single sponsor for FDA review of a new drug application totaled \$896,200 if the application contained clinical data; \$448,100 for an application not containing clinical data or a supplement requiring clinical data; \$313,100 a year for each registered establishment; and \$49,750 a year for each listed product. These fee levels are set annually based on the aggregate level of income FDA requires to maintain the full-time employee equivalents (FTEs) it hired divided by the number of applications, and establishment/product listings it expects to receive in a given calendar year.

In exchange for these fees, which have increased significantly since the program was initiated in 1992 (when they were \$100,000 per application, \$60,000 per establishment, and \$6,000

per product listed), product sponsors receive non-binding "performance goals" from FDA pursuant to a side letter and mandated Annual Reports delivered to the Congress. This side letter is not a legal performance standard mandating FDA review and action deadlines. Rather, it is a set of objectives for FDA review divisions. If the agency fails to meet these objectives, as reported to Congressional oversight committees each year, it risks Congressional and industry opposition to the reauthorization of the Prescription Drug User Fee Act (PDUFA). That reauthorization is mandated to occur in five-year increments. In the event that the law is not renewed this year in 2007, to extend the program until fiscal 2012, FDA would theoretically lose over \$300 million of annual funding. This amount supports at least 600 reviewers and many more administrative support personnel

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and systems. Industry would lose the significant leverage it maintains over FDA, through Congressional oversight, to maintain non-binding application review deadlines. Those deadlines are currently set at 10 months for standard NDAs and at six months for priority applications and supplements.

In its most recent Report to the Congress detailing the results of Fiscal Year 2006 (Oct. 1, 2005- Sept. 31, 2006), FDA stated that it received 113 new drug applications (NDAs) and biologics license applications (BLAs), down from the 129 received in fiscal 2004. Thirty-four of those applications were designated for priority review of 6-months (products to treat serious and life threatening diseases). In addition, 153 efficacy supplements were filed, 2,503 manufacturing supplements, 2,430 meeting requests and 392 special protocol assessments. FDA reported exceeding its 90 percent on-time compliance goal for FY 2006 with 95 percent of priority applications acted-on timely and 100% of standard applications.

PDUFA III, which was adopted with a variety of review reforms to expedite development of bioterrorism treatments, contained a number of other agency reforms. Those reforms included: meeting management goals (established timeframes for conducting Type A, B and C meetings); detained meeting request procedures and protocols for such meetings; and creation of a new procedure for special protocol assessments when FDA would be bound by the protocol design agreed to in pre-NDA/BLA planning sessions. Procedures similar to PDUFA II were also provided for clinical hold responses and formal dispute resolution. Additionally, FDA agreed to

conduct two pilot programs to evaluate the development of continuous marketing applications.

Medical Device User Fee and Modernization Act

In 2002, a user fee regime was also enacted for medical devices, and it is also scheduled to expire on September 30, 2007. Reauthorization will likely occur in separate legislation enacted shortly before the scheduled expiration date. User fees for medical devices supplemented FDA's direct appropriations by a reported \$40 million for FY06. These fees include only application review fees based on a standard base fee. That fee for FY07 is \$281,600 for a Premarket Approval Application (PMA) that contains clinical research. The small business PMA base fee is \$107,008. The fee for a 180-day supplement is set at 21.5 percent of the base fee (\$60,544). The small business fee is \$23,007. The fee for a real-time supplement (e.g., Changes Being Effected supplement) is set at 7.2 percent of the base fee (\$20,275).

A special small business rate exists for all applications other than PMAs equal to 38 percent of the standard fees. Fees for 510(k) substantial equivalence applications are set so the fees from all 510(k)s would produce revenue as if all were assessed a fee of 1.42 percent of the base fee. These fee rates are to be adjusted so that the fee paid by a qualifying small business (about 19 percent of 510(k) applications) is 80 percent of the full rate for the 510(k). For FY07, the 510(k) application fee is \$4,158, and for a small business, \$3,326 per application.

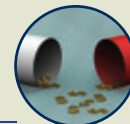
In exchange for these fees, the non-binding performance goals

agreed to by the agency in a November 14, 2002, letter to Senator Ted Kennedy (D-MA) include the following: 90 percent of FY07 submissions will comply, PMA first action deficiency letters will issue in 150 days; and 180-days for all other PMA first action letters; 120 days for second or later action deficiency letters; amendments to deficiency or not approvable letters will be acted on in 180 days. An expedited procedure for PMAs was also defined with first action in 120 days. First action on 510(k) submissions is 75 days, with subsequent action letters issued in 60 days. FDA's FY06 Report to Congress generally indicated that it will meet its 90 percent goals for FY07.

Animal Drug User Fee Act

In 2003, a program similar to PDUFA was adopted for animal drug applications. The authority to collect user fees on these applications will not expire until September 30, 2008. In FY 2006, FDA collected \$11 million for Animal Drug User Fee Application (ADUFA) and projects a similar return for FY 2007. For FY07, application fees are \$168,600, fees for supplements containing data are \$84,300, annual product fees are \$4,115, annual establishment fees are \$51,350, and a separate annual fee on all sponsors is \$44,850.





Changes Proposed for PDUFA IV

In January 2007, FDA announced the results of discussions between stakeholders, including Congress, industry, patient advocates and organizations representing health care professionals and consumers. These results reflect the outline of the components of a reauthorization of prescription drug user fees from October 2007 until September 30, 2012. According to FDA, industry representatives agreed to pay an additional \$87.4 million a year in increased fees (over and above the formulas adjusted annually based on the projected number of applications received). These proposals were presented to the public for comment in a meeting on February 16, 2007. After all public comments are evaluated, and any appropriate changes made, FDA intends to submit a final proposal to Congress for its review.

Traditionally, industry has resisted the payment of fees dedicated to matters other than application review. It has reasoned that resources used for surveillance or manufacturer compliance activities should come from government funds—industry should not be forced to pay for government oversight and compliance activities. Since implementation of the program in 1992, which was supported and advocated by representatives of the Pharmaceutical Research and Manufacturers Association (PhRMA), drug manufacturers have taken the position that user fees had to be: 1) additive to existing FDA baseline appropriations; 2) fully dedicated to the approval of new drugs and biologics; 3) reasonable amounts; 4) based on a long-term government commitment to specific improvements in the approval

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process; and 5) part of performance goals that should be established by the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) to evaluate improvements in the review and approval process.

Based on an industry desire to reassure the public concerning the sanctity of the FDA drug review process and drug safety, it appears that industry has agreed to the following annual payments to expand the user fee program:

- \$17.7 million a year to adjust the base amount of fees for inflation and increases in reviewer salaries and benefits.
- \$11.7 million a year to fund the FDA consolidation on the White Oak campus.
- \$20 million to cover significant increases in FDA's drug review workload.
- \$29.3 million to enhance FDA drug safety capabilities including: the number of FTEs dedicated to drug safety evaluation of marketed medications, adoption of new safety approaches including new systems to detect and prevent adverse events.
- \$4.6 million to expedite new drug development including new guidance on clinical trial design, work to clarify regulatory pathways in areas of predictive toxicology, biomarker qualification, the handling of missing trial data and other Critical Path initiatives.

- \$4 million to improve informational technology to move toward electronic filings and an all electronic review environment; also to help in postmarketing monitoring of the overall safe and effective use of products.

- Approximately \$6.25 million to hire 27 additional drug-marketing reviewers to provide more timely review of direct-to-consumer (DTC) broadcast advertising to be paid separately by companies that seek FDA advisory reviews.

User Fee Train: Likely Passengers

It is the hope of FDA and its negotiating partners that the legislation to reauthorize PDUFA and the Medical Device User Fee and Modernization Act (MDUFMA) will be a relatively clean bill. In other words, proponents of drug and device user fees will likely oppose the addition of any amendments that could render the legislation controversial and, thereby, impede its easy passage.

If the past is prologue, however, all the prior user fee bills carried substantive amendments unrelated to raising revenue for the agency. These amendments were sought by others on the FDA authorizing committees. This “must pass” vehicle is irresistible to proponents of more controversial provisions that might be opposed by industry, or minor provisions that would be unlikely to gain sufficient support for consideration on their own.



PDUFA I included dietary supplement provisions. PDUFA II included the entire FDA Modernization Act (FDAMA) reforming the agency's regulatory processes and interactions with regulated industry. PDUFA III included mechanisms to reduce the regulatory barriers for the development and stockpiling of new therapies to combat the threat of bioterrorism. It also created a new regime for the

requiring a representative from FDA's Office of Surveillance to participate in each product review; increased internal CDER research to assess safety data; use of a more systematic or quantified approach to risk-benefit analysis; posting all NDA packages on FDA's website; increased resources and funding for postmarket surveillance and agency risk communications; etc. While FDA is attempting to address many of these

RxUSA injunction restricting agency implementation; expediting electronic data requirements under Part 11; restrictive tissue use and screening procedures; and a list of other FDA-related issues of interest to other members of the jurisdictional committees. FDA has a history of attempting to make changes internally to preclude the imposition of proscriptive legislative requirements.. Therefore, some of these items may drop off Member wish-lists.

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prior notice of food shipments and registration of food establishments.

So, what issues await in the cue for consideration by the new Democratic majority this year in the 110th Congress? The list is long, and potentially complicated. First and foremost are a variety of provisions to increase FDA's priorities and resources related to postmarket drug safety. Proposals in the legislation sponsored by Senators Kennedy and Michael Enzi (R-WY) include: organization of a Drug Safety Oversight Board; expansion of adverse event reporting; mandatory risk evaluation and mitigation strategies as part of NDAs; database monitoring; and creation of a public-private institute for applied biomedical research.

A laundry list of additional FDA reforms was included in a recent report of the Institute of Medicine on drug safety. Those proposals included: insulating the FDA Commissioner from political considerations with a 6-year term common to independent agencies; creation of a management advisory board at the Department of Health and Human Services (HHS);

issues internally to obviate the need for proscriptive legislation, major drug safety reforms are likely to be included in PDUFA IV.

Other issues likely to be pursued by Members of Congress for inclusion in PDUFA include: a new regulatory pathway for the review of biogeneric or biosimilar biologic drug products (drawn from legislation introduced by Senator Charles Schumer (D-NY) and Representative Henry Waxman (D-CA); mechanisms to review older unapproved prescription drugs that are currently marketed; tougher rules on the regulation of certain in vitro medical devices and laboratory developed tests; revising written drug wholesaler pedigree requirements in light of the recent

Conclusion

PDUFA and MDUFMA are "must pass" bills by September 30, 2007. The leadership of the new Democratic majorities in the House and Senate will be tested in maintaining a manageable bill that contains no "poison pills" or other provisions that could block passage or signing by President Bush.

Legislation to reauthorize drug and device user fees will likely be framed as some form of drug safety and enhancement legislation. User fee resources could increase by 25 percent or more commencing in FY08 through 2012. Those additional resources, if approved by congressional appropriation committees as required, are likely to flow to new postmarketing surveillance and compliance auditing systems. Such action could further erode and divert the original focus of user fee legislation from product review to industry enforcement initiatives. ▲



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