



Congress Adopts New User Fee Program

Jill Wechsler

PDUFA III boosts manufacturer fees to support postapproval surveillance and streamline the FDA review process.

Just before leaving Washington for the Memorial Day recess, Congress approved legislation to enhance the ability of public health agencies to respond to bioterrorist threats. A key addition to the bill reauthorizes the Prescription Drug User Fee Act (PDUFA) for five years. Without the legislation, PDUFA would have expired 30 September 2002. The revised user fee program (PDUFA III) was negotiated several months ago

by representatives from the industry and FDA and was altered minimally by the House and Senate. It significantly increases fees from manufacturers to support expanded FDA operations, provides more flexibility in how the agency can use fee revenues, backs several new FDA initiatives, and streamlines drug development and approval. These actions are important for pharmaceutical and biotech manufacturers.

Continuing success

There is fairly strong agreement that the 10-year-old user fee program for prescription drugs has significantly sped up FDA's drug approval process. Total approval time for new drug applications (NDAs) has dropped from approximately 23 months (pre-PDUFA) to less than 12 months. Priority applications now are processed in six months. FDA officials also believe that overall approval rates of submissions have increased from 60% to nearly 80% because of the agency's efforts to clarify which data are necessary for submissions.

FDA has met these goals by collecting substantial fees from manufacturers. All user fees generated nearly \$135 million in fiscal year 2001 and are expected to total \$162 million this year. Combined with government appropriations, the program will provide FDA with nearly \$325 million in resources for drug review activities this year, compared with approximately \$120 million in 1992. These added resources have allowed FDA to significantly increase its review staff for drugs and biologics. By the end of this year, more than 900 new staff members will have joined the agency.

FDA concerns

However, FDA officials maintain that the added revenues have not been sufficient to support a huge work-load increase in its CDER and CBER divisions. Because the agency must spend enough appropriated funds to match user fee revenues, years of flat annual budgets have required CDER and CBER to siphon funds away from other programs to cover drug review activities. The result is that many FDA programs not covered by PDUFA have lost resources since 1992, including postmarket surveillance of prescription drugs.

This overall funding shortfall has been aggravated by a decline in anticipated user fee revenues. In the past few years, fee-paying applications to CDER and CBER have decreased because of fewer submissions and an increased number of waivers and exemptions. Unfortunately, the agency's work load has continued to grow, particularly for reviewing investigational new drug applications (INDs) and supplements. The agency can use user fee revenues to process these applications but does not collect separate fees for these submissions.

Seeking changes

To remedy these problems, FDA officials began lobbying for PDUFA revisions more than a year ago. FDA wanted to increase fees and use a portion of fee revenues to cover postapproval activities such as adverse event monitoring. At public meetings, patient advocates backed the agency's plan to expand postapproval safety activities, including the review of drug advertising. Some industry critics expressed concern that higher user fees would increase manufacturer influence over the agency and compromise FDA's independence. They said Congress should boost FDA's budget and eliminate user fees altogether, but that idea never gained much support on Capitol Hill.

Challenges to the user fee program, though, softened industry opposition to allocating fees for expanding postmarketing regulation. FDA and manufacturers began negotiations more than a year ago to develop a joint proposal to take to Congress. They sent the PDUFA III agreement to the House and Senate in March for Congress to approve the new program quickly. Although the

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user fee program wasn't scheduled to expire until the end of September, FDA would have sent out hundreds of notices this summer to warn staffers of possible work-force reductions had the program not been reauthorized. Democrat and Republican leaders basically accepted the FDA-industry plan and added it to the bioterrorism bill.

Boosting revenues

PDUFA III not only increases user fees paid by industry, but also makes revisions to put the program on sound financial footing, as sought by FDA. The new system sets specific revenue targets that FDA can adjust upward on the basis of inflation plus changes in total application review work load, including NDAs, INDs, and efficacy and manufacturing supple-

ments. In addition, the Best Pharmaceuticals for Children Act (BPCA) was signed into law in January 2002. This legislation permits FDA to collect user fees for reviewing pediatric supplements, something that had been exempt from the fee program.

The legislation calls for PDUFA III fees to total \$223 million in fiscal year 2003, and rise to \$260 million in 2007, compared with \$162 million this year. These totals are equally divided among application fees, product fees, and establishment fees (i.e., \$74 million for each group next year), which are calculated annually. The fee this year for a full NDA is \$313,000; applications without clinical data and supplements with clinical data pay half (\$157,000). Small companies filing their first NDA or biologics license application (BLA) can apply for a fee waiver.

Manufacturers can expect to see a big boost in this year's \$140,000 establishment fees. The increase will provide \$74 million for fee payments in 2003 compared with \$50 million in 2002. The legislation defines a *prescription drug establishment* as a foreign or domestic place of business that consists of one or more buildings within five miles of each other where prescription drug products are manufactured in final dosage form. Thus, it excludes packaging or noncommercial operations.

Manufacturers also pay an annual fee for each approved product on the market. This year's product fee is nearly \$22,000 and applies to an estimated 2293 prescription drugs and biologics. It does not apply to generic drugs, blood products, and certain biologics. To clarify which products must pay the fee, the revised law calls for FDA to refer to the drug product list in the *Orange Book*. Starting this year, FDA also will collect these annual fees on 1 October instead of on 1 January to gain access to these revenues at the beginning of the federal government's fiscal year.

The legislation also gives FDA more flexibility for meeting requirements to spend as much on drug review from appropriated funds as it collects from user fees. The new system gives FDA a 3-5% margin of error to avoid collecting what it spends from user fees and appropriated funds to reduce the possibility that a budget miscalculation could jeopardize the entire user fee program.

Protecting public health

The broader bioterrorism bill authorizes \$4.6 billion to fund initiatives to protect the nation against bioterrorist actions. Several initiatives affect FDA and manufacturers because they

- expand national stockpiles of drugs, vaccines, and other medical products, with specific reference to smallpox vaccines and antiviral products
- authorize grants to accelerate development of vaccines, diagnostic tests, and other priority countermeasures to bioterrorist attacks. FDA should evaluate such new and emerging technologies on a priority basis.
- require enhanced security at facilities involved in the development, production, distribution, or storage of priority countermeasures
- require researchers working with biological agents or toxins identified by HHS as potential bioterrorist weapons to register with HHS, follow security requirements, and submit to inspections.

There are waivers for approved drugs and possibly for manufacturers investigating new therapies under FDA regulations, but failure to comply could bring criminal penalties.

- mandate annual registration of foreign manufacturers that import drugs and medical devices into the United States, specifying electronic registration and application to brokers and individual importers.
- Before the ink was dry on the legislation, FDA issued a final rule that permits pharmaceutical and biotech companies to seek approval of certain vaccines and medicines on the basis of efficacy testing in animals. The policy requires routine safety testing in humans while relying on animal models to determine efficacy in preventing or treating individuals exposed to toxic substances that cannot ethically be tested in human volunteers.

Streamlining reviews

PDUFA III tackles several thorny issues related to how FDA reviews applications, although it makes very few changes in basic performance goals in this area. The agency will continue to review and act on

90% of standard NDAs and BLAs in 10 months and priority applications in 6 months. Efficacy supplements have similar time frames, although FDA hopes to reduce review times for some resubmitted supplements. For manufacturing

supplements, the agency aims to review those that require prior approval within 4 months, while retaining the 6-month review target for changes-being-effected and 30-day supplements.

One issue addressed by PDUFA III is FDA's tendency to issue more "approvable" letters to sponsors to meet user fee deadlines for "taking action" on an application. This strategy often leads to multiple review cycles, delaying final approval. The legislation calls for the following actions to address this concern:

- Notify manufacturer quickly upon review of initial filing of any substantive deficiencies or the absence of deficiencies.
- Develop guidance about CDER and CBER filing review processes, including communication with the sponsor about easily correctable deficiencies, needed planning for advisory committee meetings, and procedures for negotiating final product labeling.
- Replace the approvable action letter with a complete response letter, which informs the sponsor in detail about specific de-

iciencies remaining and actions needed for FDA to approve the application.

- Clarify procedures for a sponsor to file a major amendment to resolve deficiencies or to resubmit an original application. Resubmissions that warrant speedy review can include draft or final printed labeling; safety data updates; stability data updates to support provisional or final dating periods; assay vali-

dation data; and final release testing on the last one or two lots used to support approval.

- Evaluate FDA's first-cycle reviews to determine whether these changes improved the process. The agency will use a portion of a \$7-million new initiatives fund to assess first-cycle reviews of all NDAs and BLAs during PDUFA III to identify best practices that facilitate the

review process. FDA also will conduct a broader analysis of CDER and CBER review processes to identify the need for system redesign or process reengineering. The fund also could be used to support access to external experts and advance information management tools.

Accelerating drug development

PDUFA III offers a number of initiatives to facilitate drug testing and development. FDA will continue to meet specific time frames for holding meetings with manufacturers to discuss drug development plans. The user-fee agreement explains the action companies should take to request formal meetings and procedures for documenting meeting discussions.

The legislation also describes procedures for requesting FDA evaluation of certain protocols and issues related to clinical trial design and calls for FDA officials to adhere to an earlier agreement that a research plan will meet regulatory requirements. A new program permits manufacturers of biotech therapies to request that FDA hire an independent consultant to participate in the agency's review of a clinical trial protocol. Such requests will be available for important new treatments where there is substantial disagreement between FDA and the sponsor about a proposed protocol. In addition, the legislation establishes a more formal program for resolving disputes about procedures or scientific matters that may arise during product development or FDA review.

FDA will conduct two pilot tests of additional innovations that may accelerate development of fast-track drugs and biologics. One initiative is designed to determine whether frequent scientific feedback and interactions between the agency and sponsor would accelerate product development. The other pilot test is a rolling review process. FDA would accept certain "reviewable units" of an application before the submission of a complete NDA or BLA. FDA will develop guidances for implementing these programs and hire an outside expert to evaluate their effect on drug development and review.

Expanding postmarket surveillance

An important provision in PDUFA III authorizes FDA to use fee revenues to review risk-management plans and expand

post-marketing surveillance of new products. Its goal is to encourage manufacturers to develop risk strategies during the drug development process and discuss with FDA relevant safety information and any additional postapproval safety studies needed before filing an NDA. A risk-management proposal should assess clinical trial limitations and disease epidemiology and present risk-management tools to address known and potential risks. This includes identifying those risks that should be targeted in postapproval surveillance.

The user fee program also now will support FDA's review of a manufacturer's risk management activities during the preapproval period following approval of a new drug. This period will be two years for most products and as many as three years for products considered to be higher risk—those that require a black box or bolded warning, a medication guide, or restricted distribution. The agency also will expand its ability to use outside health information databases to independently

evaluate the use of new drugs that carry important safety concerns.

FDA may publicize the failure of any company to complete agreed-on post-marketing studies. Manufacturers that fail to complete a study may be required to notify healthcare practitioners that certain issues related to a product's clinical benefit or safety remain unanswered.

A final PDUFA III provision calls for FDA to centralize information systems that track and fund the PDUFA program. This is part of an IT infrastructure consolidation initiative for all of Health and Human Services (HHS). It would establish a centralized process for all electronic submissions involving drugs and biologics, including a Common Technical Document and other submissions to the agency.

Additional fine-tuning

Although Congress basically accepted and codified the PDUFA III agreement crafted by FDA and industry, legislators added a few provisions. One change is to require the agency to include consumer and pa-

tient advocacy groups, healthcare professionals, and academics in the next round of user fee negotiations, which will begin in about four years. FDA must publish the resulting proposal, a decision designed to address complaints that this year's agreement was developed behind closed doors.

The legislation specifically authorizes additional funding for CDER's Office of Drug Safety and its Office of Generic Drugs to expand their activities. It also boosts support for the Division of Drug Marketing, Advertising and Communications to ensure that promotional drug marketing material is not false or misleading.

Some controversial measures were dropped from the final bill. A provision to provide an antitrust waiver for manufacturers that collaborate on bioterrorism counter measures was omitted, as well as an effort to codify FDA's mandatory pediatric rules, which had become controversial in recent months. There also was a move to establish user fees for medical device makers, but that effort collapsed at the last moment. **PT**