BY KIM RIBBINK

P•D•U•F•A

STRONGER AND MORE EFFECTIVE THAN EVER

"With the additional resources and an enhanced ability to monitor safety of new drugs as they enter the marketplace we're taking a step forward in transforming the FDA into an even more efficient agency, while maintaining our high standards of safety. PDUFA will be stronger and more effective than ever."

Deputy FDA Commissioner Dr. Lester M. Crawford

As time was about to expire, Congress approved legislation reauthorizing the Prescription Drug User Fee Act of 1992 (PDUFA) for five years. The reauthorization of PDUFA was included in the bioterrorism legislation passed in May by both houses of Congress, and was signed into law by President Bush on June 11th. Without approval, PDUFA would have expired Sept. 30, 2002.

The law's provision authorizing the third five-year extension of the Prescription Drug User Fee Act (PDUFA) of 1992 is of great significance for the FDA's drug-review process. It maintains the high performance goals of PDUFA II and its accompanying legislation, the FDA Modernization Act of 1997, which included greatly reduced drug review times and increased and accelerated consultations between the FDA and the product sponsors. In addition, PDUFA III meets two major FDA goals by remedying resource shortages that have affected the program in recent years.

PDUFA III, which went into effect Oct. 1, 2002, puts the agency on sound financial basis by authorizing the collection of $1.2 billion in user fees over the next five years. This will enable the FDA to increase the staffing of the drug program by 450 full-time employees, in part to help improve risk detection, identification, assessment, and intervention, and improve working conditions and training.

In addition, the law allows for expert consultations for pivotal protocol review for biotechnology products, calls for expanded electronic submission capability and harmonization of infrastructure for submissions across the FDA's review centers, and provides for earlier feedback during application review in an effort to increase the number of applications approved on the first review cycle (see box on page 39 for more details).

Possibly even more important is the authorization to spend $70 million of the user fees to increase the agency's surveillance of the safety of drugs during the first two (or, for potentially dangerous medications, three) years on the market. It is during this initial period, when new medicines enter the market in wide use, that the agency is best able to identify and counter adverse side effects that did not appear during clinical trials. Pre-PDUFA III, the review of a new drug or biologic application was separate from post-marketing safety review, which had not been funded by user fees. Under the new act, that post-marketing safety information will be addressed at the start of the application process, and the review of any risk-management plans developed will be funded by user fees.

The elements of a risk-management plan may include: assessment of clinical-trial limitations and disease epidemiology, assessment of risk-management tools to address known and potential risks, suggestions for possible Phase IV epidemiology studies (studies done after approval of a drug), and proposals for targeted post-approval surveillance. Evaluation might include using drug utilization databases during the first three years after approval.

The increased user fees for PDUFA III will enable the FDA to hire an additional 100 risk-management officers during the five-year duration of the reauthorization. This translates into doubling the number of safety officers in

PDUFA III—What's New

The reauthorization of PDUFA III provides for a total of $223 million in fees in fiscal 2003, rising to $260 million in 2007. In addition to hiring more than 450 new FDA staff members, the funds will be allocated to several other initiatives, some of which are highlighted below.

CONTINUOUS MARKETING APPLICATION (CMA)

Key features under CMA are two pilot programs, a guidance to be published by fiscal year 2004, restricted to fast-track products, and evaluation by a third party.

The first pilot program is discipline review letters for pre-submitted "reviewable units" of NDAs/BLAs. In this case, the product has had an end-of-phase 2 and/or a pre-NDA/BLA meeting, and demonstrated significant promise as a therapeutic advance in clinical trials. The FDA may enter into an agreement with the sponsor to accept pre-submission of one or more "reviewable units." There will be a discipline review letter on the individual "reviewable unit" from the discipline review team, (not final, definitive decisions) within six months of receipt.

The second pilot program is frequent scientific feedback and interactions during drug development. The pilot program is limited to one fast-track product in each review division during the pilot program. The product has had an end-of-phase 1 meeting, and the FDA may enter into an agreement with the sponsor to initiate a formal program of frequent scientific feedback and interactions regarding the drug-development program.

INDEPENDENT CONSULTANTS

During the development period for a biotechnology product, a sponsor may request that the FDA engage an independent expert consultant, selected by the FDA, to participate in the agency's review of the protocol for the clinical studies that are expected to serve as the primary basis for a claim.

Guidance is to be developed, and there will be an evaluation of the program.

Conditions are that it is a specified biotechnology product that represents a significant advance in the treatment, diagnosis, or prevention of a disease or condition, or has the potential to address an unmet medical need.

Also there needs to be a written request submitted in conjunction with a formal meeting request.

PRE- AND PERI-NDA/BLA RISK-MANAGEMENT PLAN ACTIVITIES

Key features of the risk-management plan include submission and review of pre-NDA/BLA meeting packages; pre-NDA/BLA meeting with applicant; review of NDA/BLA; peri-approval submission of observational study reports; and periodic safety update reports.

FIRST CYCLE REVIEW PERFORMANCE

This program involves notification of issues identified during the filing review, good review management principles guidance, training, and evaluation.

IMPROVING FDA PERFORMANCE MANAGEMENT

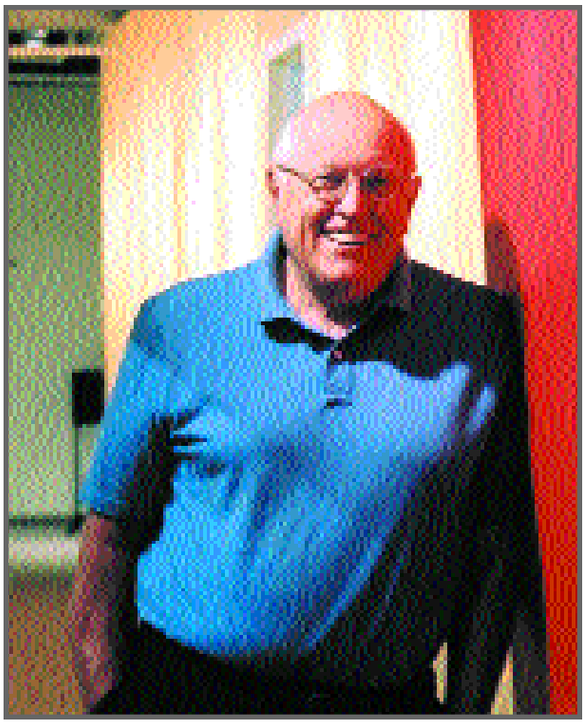
The program will have a performance fund of $7 million over 5 years and will be administered by the commissioner. It will fund studies aimed at gathering information on review performance.

The first two initiatives are: first cycle review performance; and process review and analysis.

ELECTRONIC APPLICATIONS AND SUBMISSIONS

The agency will centralize accountability and funding. Goals include: implementation of a common solution for secure exchange of content; single point of entry for receipt of all electronic submissions; and providing a specification format for the electronic submission of the common technical document (eCTD). Quarterly briefings on IT issues will be chaired by the agency CIO.

Source: Robert A. Yetter, Ph.D., associate director for review management at the Center for Biologics Evaluation and Research.



HARRY SWEENEY

IF SAFETY ISSUES ARISE THERE IS A MECHANISM IN PLACE TO GET AN EARLY WARNING ON WHAT THOSE ISSUES ARE.

the FDA's Office of Drug Safety. The extra staff will allow the FDA to more actively monitor the risk-management plans, which will be specifically tailored to each drug application.

"FDA views this as an important step to improving our ability to manage the risks and improve the safe use of approved drugs," says John K. Jenkins, M.D., director of the Office of New Drug Safety, FDA, Center for Drug Evaluation and Research. "For the first time FDA will be able to use user fees to pay for post-marketing safety activities, such as review of adverse event reports. It is anticipated that the new user fees will allow FDA to double the size of its drug safety staff during the next five years. This should have a significant impact on drug safety since the agency and sponsors will be focusing increased efforts on managing the risks of drugs during the pre-approval and first few years post-approval."

The new amendment not only impacts the regulatory agency but has direct implications for pharmaceutical and biotechnology manufacturers in making them more accountable.

"The benefit of this legislation is that it finally puts teeth into the tacit expectation that pharma will take responsibility for the use and risks of drugs after marketing," says Judith Jones, M.D., Ph.D., president and CEO of The Degge Group. "Although pharma is responsible and liable, the new legislation is explicit, with clear expectations for actions and evaluation of the effectiveness of those actions to manage risk."

Some industry experts say post-marketing surveillance will be good for all stakeholders, including companies, because the initiative provides a systematic process to evaluate Phase IV, which had been absent in the past.

Robert B. Naso, Ph.D., senior VP of quality regulatory and product development at Nabi Biopharmaceuticals concurs. "One of the problems the FDA always has had with Phase IV obligations is that many pharmaceutical companies said they would conduct some type of post-approval study, but never did. If we're saying there's value to companies performing Phase IV studies and safety follow-ups post approval, we clearly must understand that the FDA has to be able to review the outcome of those studies and to monitor those studies, and clearly that adds cost to the agency."

There is a general consensus among industry experts that the additional funding to enable the monitoring of post-marketing safety surveillance was necessary.

"PDUFA III incorporates recognition of the need to have monitoring for several years post marketing so that there's mandatory feedback and collection of data during that immediate period," says Harry Sweeney, chairman and CEO of Dorland Global Health Communications. "That way, if safety issues arise, there is a mechanism in place to get an early warning on what those issues are."

While the PDUFA III agreement on performance goals does not give the FDA any additional authority to mandate post-marketing studies, it does expand the FDA's authority to utilize user fees to cover regulatory activities in the post-marketing period, such as evaluating product utilization and the implementation of risk management for drugs and biologicals with safety concerns.

"The goal of PDUFA I was to get faster, more predictable reviews of drug applications to counteract the drug lag without spending a lot of additional taxpayer money," says Christopher Milne, DVM, MPH, J.D., assistant director of Tufts. "PDUFA II went the next step and looked to enhance the environment of the FDA's response and communication with industry. PDUFA III adds to that by evaluating what happens during the life of a drug, what happens to drug utilization, what happens in the so-called periapproval stage. It will look at the whole consumer side, including safety and the limitations of the clinical-trial process."

While the issue of post-approval surveillance might lead to a greater number of companies being asked to conduct Phase IV trials, there are potential benefits, including the possibility of forging closer relationships with physicians.

"More companies are going to be required, as standard practice, to do at least one Phase IV program once a drug is approved, especially if it is approved in a more rapid time frame than the traditional time frame of five to seven years," says William Van Nostrand, president of the clinical division of Dendrite. "While that will have a huge impact on the industry in terms of costs, there are potential benefits. One of those benefits is if physicians have a good experience as a result of that Phase IV trial, they're going to continue to use that product. Physicians will learn how to use an individual product on an individual patient, helping to bring about better medicine."

Enhancing the physician relationship with an individual product can certainly help companies from a marketing standpoint.

CARY GARNER

DATA ON THE FDA'S WEBSITE INDICATE THAT SINCE PDUFA WAS APPROVED, THE WITHDRAWAL RATE FOR DRUGS HASN'T CHANGED.

THE IMPACT OF MANDATORY POST-APPROVAL, OR PHASE IV TRIALS, IS INCREASED COSTS TO SPONSORS AND INCREASED RESOURCE REQUIREMENTS.

"Post-marketing studies are going to mean more expense for the pharmaceutical industry, but from a marketing perspective it will bring greater legitimacy to Phase IV clinical studies," says Jim Clifford, co-chairman of CommonHealth.

Properly enacted and followed through, the amendment should help more than it hurts.

"In the end, all three major affected parties should benefit," says Patrick Durbin, VP and general manager of periapproval services at Covance Inc. "The regulatory agencies should more efficiently and effectively be able to review applications and follow-on trials post approval and the industry should be able to bring safe, effective drugs to market more efficiently, and patients should benefit from both."

JULIET SINGH

Industry experts caution, however, that none of this will happen overnight. "In the short term, it is doubtful that post-approval surveillance will speed up the process, since there are too many uncertainties about the meaning of risks, the ways to best manage them, and measure the impact of that management," Dr. Jones points out. "However, over time, if these processes become more routine and/or they are geared to changes in the healthcare system, they might help speed the review process. But this likely will take years."

Annette Stemhagen, Dr.PH., VP of strategic development services and periapproval services at Covance agrees that all parties should benefit from the new law. "The FDA's new focus on risk management looks at all the activities related to getting all of the stakeholders, meaning not only the drug industry, but the practitioners and the patients, involved in protecting the public health and in ensuring patients are using drugs correctly."

EVALUATING THE IMPLICATIONS

There is widespread support for the ongoing goals and new initiatives of PDUFA III, but the jury is out as to what increased surveillance will mean for the industry. The possibility that the FDA might require Phase IV studies has been around for some time. And, while the industry applauds the mission and goals of PDUFA III and the fee increase, potential periapproval clinical requirements raise some questions and concerns. No product is entirely safe, so industry insiders say the FDA's decision to require a Phase IV trial for a particular drug needs to be considered carefully. The challenge will be for the FDA and sponsors to develop better communication channels to ensure that risk-management programs are reasonable, don't delay product availability, and don't interfere with the practice of medicine.

NEHL HORTON

"Asking for Phase IV isn't harmful so long as it doesn't become a general requirement for every product that comes along, whether it's needed or not," says Ken Berkowitz, a healthcare industry consultant who provides counsel to the industry on a variety of FDA, healthcare, and public-affairs issues. In 1992, Mr. Berkowitz chaired the joint user fee PhRMA/BIO staff task force that worked with the FDA to develop PDUFA. "As long as the FDA doesn't do that under pressure from Congress and other groups, then there's nothing wrong with Phase IV. I don't see any sign of that happening, but that's always a concern that once the FDA does something it will become a general requirement."

Dr. Naso agrees, saying, "Phase IV trials should really only be required where there is some significant concern about safety, or some significant area of doubt about safety, and the FDA believes these types of studies would be necessary to generate more information. I'm not suggesting that costs should outweigh safety concerns, but there should be an element of caution with regard to the types of Phase IV studies that might be required. I don't see too much in PDUFA that provides guidance to the FDA with regard to the types of studies, the size of studies, and the duration of studies that the agency might require."

Should PDUFA lead to substantially more Phase IV requirements, the industry will have to contend with several factors.

"The negative impact of mandatory post-approval, or Phase IV trials, is increased costs to sponsors and increased resource requirements, which may not necessarily provide additional useful information or data," says Juliet Singh,

PDUFA IS A MODEL OF PUBLIC/PRIVATE PARTNERSHIP THAT PROVIDES SIGNIFICANT HEALTH BENEFITS FOR THE AMERICAN PEOPLE.

THE CHALLENGE FOR THE FDA IS TO TRY TO COME UP WITH UNIFORM AND RATIONAL WAYS TO MONITOR THE SAFETY OF DRUGS AFTER THEY'RE APPROVED.

Ph.D., VP of regulatory affairs and quality assurance at Collateral Therapeutics Inc. "But the positive side of Phase IV trials is the generation of additional safety data, expansion of indications and patient populations, and avoidance of large clinical trials."

The agency's goal is to ensure companies adhere to current good manufacturing practice (cGMP) for pharmaceutical products. In doing so the FDA seeks to eliminate, or at least minimize, potential risks to public health. But, say some industry sources, there does need to be a balance between risk and the potential reward of a curative drug.

"The agency is under a lot of pressure on one hand to get new drugs out and on the other hand to be on the safe side, and it's unclear where the pendulum is right now," says Wayne L. Pines, president of regulatory services and healthcare at APCO Worldwide. "Certainly over the past two or three years, the agency has been much more conservative in terms of new drug approvals, insisting on more data and putting companies through an additional cycle or two of review."

As the industry, Congress, and the FDA move forward with PDUFA III, all entities will have to weigh what is in the best interest of the public, in terms of safety, availability, and cost.

"The challenge for the FDA is to integrate the new post-marketing surveillance programs into new risk-management programs to try to come up with uniform and rational ways to monitor the safety of drugs after they're approved," Mr. Pines says. "That's a great challenge, because once a drug is approved, there is a loss of control. It's very difficult to gather information, to get good information, and it's virtually impossible to get comprehensive information."

Introducing risk-management programs and assigning funds to those programs alters PDUFA's original goals.

"The implications may be fairly broad, since this tends to shift the focus from efficacy and benefit to risk and benefit, and the implication is that companies will need to do careful planning that includes risk management as part of the approval package," Dr. Jones says. "Further, this planning will require consideration of interventions far beyond labeling and simple education programs for physicians to assure that the drugs, once released, are used to maximize benefit, minimize risk."

ANNETTE STEMHAGEN

WAYNE PINES

STREAMLINING THE PROCESS

Before 1992, taxpayers paid for product reviews through budgets provided by Congress. Under PDUFA, the industry provides a portion of this funding in exchange for FDA agreement to meet drug-review performance goals, which emphasize timeliness. Any time a company wants the FDA to approve a new drug or biologic before marketing, it must submit an application along with a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed.

"There's no question that added resources have made a marked difference to the review process at the FDA since PDUFA I was enacted in 1992," says Alan Goldhammer, Ph.D., associate VP for regulatory affairs at PhRMA. "The issue of adding extra resources, without changing the underlying regulatory structure — drugs need to be approved on the basis of safety and efficacy — leads both industry and the FDA to hope that the process will run more smoothly."

While the FDA's chief concern is safety, it too views the new act as possibly helping to further cut review and approval times.

"The increased resources under PDUFA III, along with some of the new pilot programs — Continuous Marketing Applications — are expected to allow the FDA to meet the PDUFA goals for review and to improve the efficiency of drug development and review," Dr. Jenkins says. "Shorter review times and an increased ability of FDA staff to interact with sponsors during the IND and NDA/BLA phase may translate into shorter times to approval."

Since PDUFA was first enacted, PhRMA estimates that the pharmaceutical industry will have paid $980 million in user fees by the fall of 2002. And despite recent concern that review times have slowed, the fees have enabled the FDA to pay the salaries of more than 1,000 highly qualified reviewers and to cut the average review time.

In 2001, pharmaceutical and biotechnology companies added 32 new treatments to the nation's medicine chest — 24 drugs and 8 biologics, according to PhRMA. The 24 drugs approved in 2001 were reviewed by the FDA in an average of 16.4 months, and the 8 biologics were reviewed in an average of 19.6 months. This represents a slight improvement over review times in 2000 — when review times for drugs and biologics were 17.6 months and 25.8 months respectively — but approval times for both drugs and biologics in 1999 and 1998 were somewhat shorter.

"User fees were adopted after rigorous discussion and debate within the industry because it was an essential means to provide resources to the agency to hire scientific, toxocological laboratory personnel," Mr. Berkowitz says.

THE FDA'S NEW FOCUS NOT ONLY LOOKS AT THE DRUG INDUSTRY, BUT THE PRACTITIONERS AND THE PATIENTS INVOLVED IN PROTECTING THE PUBLIC HEALTH AND ENSURING PATIENTS ARE USING DRUGS CORRECTLY.

WILLIAM VAN NOSTRAND

ONE BENEFIT IS IF PHYSICIANS HAVE A GOOD EXPERIENCE AS A RESULT OF A PHASE IV TRIAL, THEY'RE GOING TO CONTINUE TO USE THAT PRODUCT.

Even with shorter review times, safety has not been compromised during the tenure of PDUFA.

"No data during the life of PDUFA have shown that decreased review times have in any way increased the number of drugs withdrawn," says Cary Garner, VP and general manager of Phase IV at Parexel. "Data on the FDA's Website indicate that since PDUFA was approved, the withdrawal rate for drugs hasn't changed. It's still 2.7%, even though the approval cycle has gone from 30 months to 12 months."

The cut in review time has helped push the U.S. to the forefront of the world pharmaceutical market.

"Supporting the FDA in the review of drugs through user fees has had a very positive impact on the agency's more rapid response to new drug applications and probably has helped pull the U.S. into the forefront of drug research and accessibility of products for patients," Mr. Clifford says. "One only has to look back 10 years when products were introduced into Europe first and sometimes we didn't get them here for 7 to 10 years. It's not all because of user fees, but that has played a significant part in the turnaround."

With the enactment of PDUFA, U.S. companies overtook their European counterparts and now have a commanding lead in world markets. According to a July 2001 report in the Financial Times, the European share of the world pharmaceutical market fell from 32% to 22% during the past 10 years while U.S. market share rose from 31% to 43%. During this period, pharmaceutical R&D investment doubled in the European Union, while U.S. R&D increased five-fold.

LOUIS MORRIS

IF IT MEANS MAKING SURE THAT PEOPLE AREN'T HURT THEN COST IS JUSTIFIED, AND COST IS GOING TO BE A SECONDARY ISSUE.

"PDUFA is a model of public/private partnership that provides significant health benefits for the American people, while maintaining rigorous drug approval standards," says Nehl Horton, senior director of corporate media relations at Pfizer. "Just a decade ago, the average FDA review of a new drug application took about two and one-half years. Patients in the U.S. watched as drugs that could alleviate their diseases or conditions — or even save their lives — were approved in other countries many months or years before they were available in the U.S. With the passage of PDUFA in 1992, and its reauthorization in 1997 and 2002, that unfortunate situation has changed."

One of the primary goals of PDUFA has been to set time frames in which the FDA will review applications. The agency commits to acting on 90% of standard NDAs in 10 months and 90% of priority NDAs in six months.

"This is placing a great deal of pressure on FDA reviewers to work hard and quickly," says Alberto Grignolo, Ph.D., senior VP of worldwide regulatory affairs at Parexel International.

FDA officials also have noted that these commitments have placed certain pressures on the agency. According to the FDA, assuring that enough appropriated funds are spent on the process for the review of human drug applications to meet requirements of PDUFA, and at the same time spending resources in a way that best protects the health and safety of the American people has become increasingly difficult.

"We did see a slight slowdown in drug reviews over the last 18 months and the FDA did make a persuasive case that in part that was a result of a lack of resources within the agency," Dr. Goldhammer says.

Employing more reviewers and improving the application process, it is hoped, will ease those burdens.

"The way to cut down the time to review applications is to have more staffers to review the documents, and also automate the process and allow for more electronic review of data," Dr. Stemhagen says.

The expectation is that by increasing by 450 the number of reviewers, current time frames can be met. But some warn it might be some time before those reviewers are, firstly hired, and secondly brought up to speed. And, in the early goings, new staff may actually slow the process.

"Whenever there is an infusion of new people into any situation, there's going to be inherent inefficiencies," Mr. Pines notes. "The next year or two has the potential to be a difficult time for the industry, until the new people are fully on board. One of the difficulties companies face is when the FDA reviewer overseeing their drug changes. When that happens, there is a possibility of the new person being inexperienced or having a different perspective, and some of commitments that previously were made might not be adhered to."

Adhering to review time frames and bringing drugs to market more rapidly are just part of the problem for industry. The FDA notes that while fewer drugs have been approved in recent years, that was not the result of any decrease in performance by the agency. Rather approvals are determined, in part, by the number of new drug and biologics applications filed by companies. While the number of standard applications filed has been steady, the agency says the number of priority applications dropped sharply in 2001.

The sharp increase in fees, however, will increase pressure on the FDA to ensure it meets its stated timelines.

"FDA has done pretty well for the past 10 years," Dr. Grignolo says. "From PDUFA I to PDUFA II the agency is performing better than before PDUFA, thereby justifying industry's continued support of the program. As PDUFA III gets under way, the industry and Congress will expect these timelines to be met or else there will not be a PDUFA IV."

"PDUFA has worked extremely well for the agency and the industry, and ultimately for the consumer because it has provided the agency with the resources necessary to cut the review time down," Mr. Garner says. "PDUFA has actually been a very good example of industry, agency, and the government working together to solve a problem."

In the meantime, the FDA also is having to contend with not having a full-time commissioner. While this does pose concerns over stability within the agency, most believe PDUFA is so entrenched that there is unlikely to be any backlash once a new commissioner is named.

"Commissioners have a lot to do in terms of

THE IMPLICATION IS THAT COMPANIES WILL NEED TO DO CAREFUL PLANNING THAT INCLUDES RISK MANAGEMENT AS PART OF THE APPROVAL PACKAGE.

leadership and policy, but not in terms of day-to-day activities," says Louis A. Morris, Ph.D., president and founder of Louis A. Morris & Associates. "There's no question that not having a commissioner is a concern, but in this particular instance I think the FDA is proceeding in a pretty straightforward fashion."

BOOSTING FEES

Before the latest renewal of PDUFA, the FDA noted that the fees it had collected during PDUFA II were significantly less than expected due to the reduced number of new drug applications and the increased proportion of applications where fees are waived. The hope is that the latest renewal of PDUFA will give the FDA the resources to further improve its operations and efficiency. Fees for PDUFA III are assessed on certain types of applications and supplements for the approval of drug and biological products, certain establishments where such products are made, and certain marketed products. The FDA has announced that its rates for prescription drug user fees for fiscal year 2003 are $533,400 for an application requiring clinical data, and $266,700 for an application not requiring clinical data or a supplement requiring clinical data. Establishment fees are $209,900, and product fees $32,400. The fees are effective from October 1 until September 30, 2003, after which fee revenue amounts will be adjusted for inflation and to reflect changes in workload for the process for the review of human drug applications. Where certain conditions are met, the FDA may waive or reduce fees.

"While there could be short-term implications with the high application fee, in the long term it will be to the benefit of the industry and the patients because products that are safe and effective are able to get to patients more quickly," Mr. Berkowitz says. "That should mean companies are able to make back that money from the fees in a much more reasonable time frame."

JIM CLIFFORD

The FDA does not see increased fees as an undue burden upon the industry, especially when put into the context of the amount it costs to research and develop a pharmaceutical or biologic.

"The total amount of user fee revenue represents significantly less than 1% of total expenditures for the pharmaceutical industry and is not expected to have any impact on the cost of new drugs," Dr. Jenkins says.

Arduous or not, the higher fees and potential costs from Phase IV trials as a result of increased post-market surveillance do pose the question, who pays?

In the case of smaller companies already battling with tight profit margins, there is the likelihood that increased costs will be passed on to the consumer to some degree.

"The kinds of costs associated in general with PDUFA are not insignificant for small pharmaceutical companies," Dr. Naso notes. "For a company such as ours, a $500,000 payment to the FDA to review a BLA or NDA is a pretty big chunk of cash, and can make the difference between a profitable year and a non-profitable year. Then a large Phase IV safety follow-up study, which can be two or more years, can be a very expensive possibility. These all add costs that will come back to the consumer."

Others agree that it could cost the consumer but note that greater surveillance is to the benefit of patients, allowing them to feel more confident about the safety of a product.

"Increased user fees will help the consumer feel that as drugs are approved there will be greater surveillance, or oversight, of how the medicines are prescribed, how they're distributed by the pharmacies, and how they should be taken by patients," Mr. Van Nostrand says. "There's no question that there's going to be increased costs to do this, but the increased costs are supposed to be for the benefit of the patient."

The burning issue is can the costs be justified?

"We have to recognize that the money to do anything has to come from somewhere," Dr. Naso notes. "Costs have to go back to the consumer and/or out of the profits of a company. And the companies are owned by shareholders, who are both consumers who want safe and effective drugs, and investors who want a fair and fast return on their investment. Therefore, somebody's going to pay."

JUDITH JONES

Some experts, however, warn that recent reports criticizing the pharmaceutical industry's pricing policies make it difficult for companies to pass further increases on to the patient. In June, Express Scripts, one of the nation's largest pharmacy benefits managers reported that prescription drug spending in 2002 is expected to rise 15.9%, driven by higher prices and increased usage. According to the report, overall drug price inflation totaled 5.5% in 2001, topping 5% for the fourth consecutive year.

"The pharmaceutical company is going to be required to take a big brunt of this," Mr. Van Nostrand says. "The price tag to the patient will be higher over time, but not proportionate to the user fees and what the pharmaceutical companies have to spend. In other words, I think the profit margins are going to come down on the products. The industry will have to be more price sensitive to the consumer."

Even if it turns out that industry is forced to absorb the majority of the increased costs, there are potential silver linings in terms of money saved elsewhere.

"If the work that's required post-approval potentially helps mitigate or eliminate product withdrawals or product liability lawsuits, I would think PDUFA III, if executed properly by the FDA and the industry, may be to the industry's financial advantage," Mr. Durbin comments. "Every product that comes out has a liability associated with it, and product liability risks can run into the hundreds of millions of dollars. In certain cases, there probably could be some benefit in mitigating or avoiding that situation."

ONE ONLY HAS TO LOOK BACK 10 YEARS WHEN PRODUCTS WERE INTRODUCED INTO EUROPE FIRST AND WE DIDN'T GET THEM HERE FOR 7 TO 10 YEARS.

According to Mr. Durbin, "User fees are both economic and noble — both elements of what a pharmaceutical company exists for — since it improves patient health globally and delivers value for shareholders. If a company gets a safe, effective drug to market faster, that means that the product has a longer selling life and treats more patients for a longer period of time."

Others in the industry believe that any potential savings from getting products approved sooner are likely to be mitigated by increased costs from post-market studies and surveillance.

"People think that pharmaceutical companies have unlimited resources, but that's not true," Dr. Morris says. "But again because it's the basic safe use of the drug, resources have not been perceived as a major issue. They clearly are, but if it means making sure that people aren't hurt then it's perceived to be justified, and cost is going to be a secondary issue."

"A lot of the costs in drug development today are, some argue, related to the regulatory nature of what companies are doing," Mr. Durbin adds. "There's an imperative within the pharmaceutical industry to drive costs out of development, without cutting corners, and continuing to do safe, effective trials using technology more efficiently. Companies would argue that if the regulatory process was more efficient, that should help them."

A recent study authored by Joseph A. DiMasi, Ph.D., director of economic analysis at the Tufts Center, determined that cutting development and regulatory review times by 25% would lower total costs by $129 million, while a 33% reduction in development and regulatory review time would decrease average capitalized cost per approved new drug $167 million. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

Experts on this topic

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