BY DENISE MYSHKO

# A More Efficient FDA for the DEVICE WORLD

**QUICKER REVIEW TIMES** are an expected result of user fees, but in the evice industry they provide a uable resource as the sector loys **TECHNOLOGICAL NCES AS PART OF MISSIONS**.

IF USER FEES WORK FOR PRESCRIPTION DRUGS, THEY CAN WORK FOR MEDICAL DEVICES. That is the thinking behind the user-fee program for medical devices approved last October. Patterned after the popular prescription drug user-fee program that brought increased resources to the Food and Drug Administration as a way to help it achieve greater efficiency, the program for medical devices has a much larger goal than reducing regulatory review times.

The objective is to provide the agency with the necessary resources to address increasingly innovative and complicated medical devices stemming from technological advances in genomics, proteomics, and nanotechnology. While the real impact is not expected to be felt immediately, experts say, these advances are likely to pose significant challenges for regulators and manufacturers and could well result in a higher level of regulatory scrutiny. Increased FDA efficiency will be needed to get these products through the approval process and to market as quickly as possible.

"The medical diagnostic user-fee act was a forward-looking program to consider what it

and the
ɔringing
et in the
egulato-
y submissions, reimbursement, and govern-
ment affairs, at Roche Diagnostics.

Device review times, while longer than statutory requirements, have not been as long as those on the drug side, before the advent of user fees. Even so, in August, the FDA announced new goals to reduce the total amount of time that medical devices remain under review by the agency.

This announcement, which is part of the FDA's strategic action plan, represents the first time that the agency has publicly committed to reducing total review times for medical-device products. This complements the agency's commitment under The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) to reduce cycle and decision times for all new device reviews.

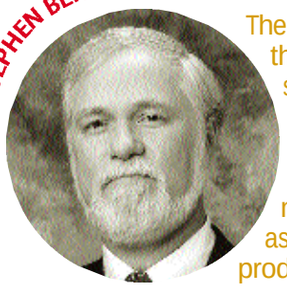
For both expedited and traditional premarket approval applications (PMAs) — the equivalent to the new drug application (NDA) on the drug side — the FDA is committed to reducing its review time by 30 days for the fastest 50% of those applications approved for fiscal years 2005 through 2007.

"I welcome the initiative because I believe the agency is going in the right direction," Mr.


RICHARD NAPLES

The FDA and the industry want the same thing. The challenge is for both to clarify what the requirements are to improve new technologies.

Naples says. "Regulators are trying to take a quality-system approach to new submissions. What that means is that they're going to work more closely with sponsors to help them bet-




There is no question that the FDA is scrutinizing device applications more rigorously. The process will become more complicated as high-margin products emerge.

ter understand what the requirements are beforehand. This will improve the quality of the submissions and by doing that, regulators can further shorten review times."

Part of the FDA's initiative is to provide greater guidance to industry.

"Many of the FDA's reviewer requirements are not written in the form of a regulation," Mr. Naples says. "In many cases, there's no specific guidance for new technology. The FDA is going to work more proactively with the sponsors of a submission to help write a guidance to review those products in a consistent and efficient manner in the future."

The new initiative is a positive in another way — it helps both the industry and the agency navigate the application process in an era of increased regulatory scrutiny.

But Stephen A. Bent, who founded the life-sciences practice at the law firm Foley & Lardner, and who now heads the firm's interdepartmental life-sciences practice, says the product approval path for devices is not going to be as easy as it was in the past.

"There's no question that the FDA is going to scrutinize device applications more rigorously," he says. "I think there are going to be more complicated, higher-margin device products coming out. Because of that, the device sector will begin to bear the same type of scrutiny that the drug companies have had to deal with for years."

## Concerns Going Forward

Most industry experts agree that the user-fee law is a positive for the medical-device industry, although there is some concern about the rate of increase for the fees.

Already fees have gone up for the second year of the program. In July 2003, the FDA announced a shortfall in the total amount of fees collected in fiscal year 2003; fees collected are about $5.5 million off target.

# A Snapshot of the DEVICE INDUSTRY

### Revenue by Market
(Dollars in millions)

| | 1999 | 2000 | 2001 | CGR %* |
|---|---|---|---|---|
| **Worldwide** | $157,800 | $168,400 | $179,800 | 6.7% |
| **United States** | 66,700 | 71,400 | 76,400 | 7.0 |
| **European Union** | 42,000 | 44,500 | 47,100 | 6.0 |
| **Japan** | 23,400 | 24,600 | 25,800 | 5.0 |
| **Rest of the World** | 25,700 | 27,900 | 30,500 | 10.0 |

### Revenue by Sector
(Dollars in millions)

| | 1999 | 2000 | 2001 | CGR %* |
|---|---|---|---|---|
| **Diagnostic (*in vitro*) products** | $20,070 | $20,290 | $20,490 | 1.0% |
| **Minimally invasive surgery prod.** | 13,800 | 14,900 | 16,400 | 9.0 |
| **Orthopedic products** | 11,700 | 13,100 | 14,700 | 12.0 |
| **Wound-care products** | 10,400 | 11,600 | 13,000 | 12.0 |
| **Ophthalmic devices** | 11,500 | 11,800 | 12,100 | 2.5 |
| **Cardiovascular devices** | 10,500 | 11,500 | 12,500 | 9.0 |
| **Diagnostic imaging products** | 10,300 | 10,600 | 10,900 | 3.0 |
| **Dialysis products** | 7,500 | 8,000 | 8,700 | 8.0 |
| **Dental products** | 6,300 | 6,800 | 7,300 | 8.0 |
| **Lasers (medical)** | 1,950 | 2,250 | 2,600 | 15.0 |
| **Patient-monitoring devices** | 2,100 | 2,200 | 2,300 | 5.0 |
| **Hearing-aid devices** | 1,800 | 2,000 | 2,150 | 9.0 |
| **Respiratory devices** | 1,700 | 1,750 | 1,800 | 3.0 |

Note: CGR% = compound annual growth rate

Source: The Medical & Healthcare Marketplace Guide, 18th edition, published by Dorland Healthcare Information. For more information, visit dorlandhealth.com

## Medical Device FACTS

- U.S. production of device and diagnostic products was valued at $80 billion in 2001, an increase of 5.6% from the year before. Of that, medical devices accounted for $68.7 billion and $11.3 billion for diagnostic products.
- Industry R&D expenditure, as a percentage of sales, in 1999 was 12.9%.
- The United States is the largest producer of medical devices and diagnostics, with production of $80 billion in 2001. The United States also is a large exporter of medical devices.
- There are about 6,000 medical-device and diagnostic companies in the United States, of which more than half were involved in manufacturing surgical and medical instruments, appliances, or supplies.
- More than 130,000 types of medical devices are used in hospitals, outpatient facilities, clinics, physician practices, and other sites for the diagnosis and treatment of medical conditions.

Source:
Advanced Medical Technology Association (AdvaMed), Washington, D.C.
For more information, visit advamed.org.

This will mean an increase in fees for fiscal year 2004, which began Oct. 1, 2003.

By statute, all fees are set in proportion to the fee for a full PMA. Fees for 180-day supplements and real-time supplements are 21.5% and 7.2%, respectively, of the full fee for PMAs.

Fees for 510(k)s — the application process for devices that are similar to products already on the market — are 1.42% of the full PMA rates. Small businesses are entitled to reduced fees for both PMA and 510(k) applications, and the FDA anticipates that about 80% of companies that submit 510(k)s will qualify for the small business rate in fiscal year 2004.

ED MARCH

The biggest problem the industry always has had is lack of regulatory guidance. It's very tough for manufacturers to establish a path for clearance or approval.

Also in fiscal year 2004, a two-tier fee rate for 510(k)s goes into effect for the first time. Unlike the prescription-drug review process, medical devices are classified based on the risk to patients. The most regulated devices are in Class III, which requires clinical-trial data to support any claims made by the manufacturer about the device. (See box on page 40 for more information.)

"There will be a great deal of concern if the fees rise and the review time by the FDA doesn't go down," says Michelle Kile, a partner at Foley & Lardner. "It may be a couple of years, though, before post-MDUFMA data can be fairly compared with pre-MDUFMA information."

According to the FDA, for fiscal year 2002 — the year before user fees were collected — the total average review time for devices increased to 213 days from 172 days in fiscal year 2001.

Agency officials say the total elapsed time from submission to decision in fiscal year 2002 decreased from 411 days in fiscal year 2001 to 364 days in fiscal year 2002.

For devices evaluated as a 510(k) product, the total average review time increased to 100 days in fiscal year 2002 from 96 in fiscal year 2001, and the average FDA review time was 79 days, up from 75 days in fiscal year 2001.

User fees are an unfair burden to smaller device manufacturers, says Mark B. Leahey, executive director of the Medical Device Manufacturers Association (MDMA).

"There were steps short of a user fee that could have been implemented," he says. "But unfortunately that dialogue was never able to occur because there were certain large manufacturers that bulldozed this law through without checking with the rest of the industry. There was no public hearing. We support efforts to increase FDA funding, but government regulators should be funded by the government, not by the industry."

One of the biggest issues is the definition of a small company, Mr. Leahey says.

"Many people use PDUFA as the model in the device world," he says. "In the drug world, a small business is a company with 500 or fewer employees. We said that same definition should be applicable to the device world. The large device manufacturers fought this tooth and nail. They wanted to treat a $5 million company the same as a $5 billion company. Ultimately, the definition of a small company is one with less than $30 million in revenue. This probably equates to about 125 employees. For these companies, the user fee represents the need for a considerable number of full-time employees who could be helping to develop a new product."

Some experts also point out that most of the improvement in review times of 510(k)s — which is close to statutory requirements — was accomplished before user fees were put into place. The median review time, i.e., the time it took the agency to review 50% of the 510(k)s, has been falling from a high of 164 days in fiscal year 1993 to 74 days in fiscal year 2002.

According to Neal Fearnot, president of Med Institute Inc., user fees are not likely to further reduce review times.

"The user-fee legislation has had an important role in getting the review times down, but not in the way people think," he says. "Regulators first asked for user fees at a time when review times were even longer. Without the user fees, FDA officials were forced to look at allocating their remaining resources, which helped them to make decisions to exempt a large number of classes from review."

For PMAs, he says, the user-fee law is unlikely to have much of an impact.

"The process for reviewing a PMA is scientifically based," Mr. Fearnot says. "The major problems with the PMA process are not necessarily review-time oriented. Some like to think that user fees are a magic bullet, but that's not true. The vast majority of the time required to obtain PMA approval is based on the number of preclinical and clinical tests required. User fees likely will have no impact on those."

AMIT BOHORA

The device industry is quite efficient right now. Device manufacturers are doing the best they can. There is a bottleneck and that bottleneck is FDA review.

For these products, Mr. Fearnot says what is needed is more careful consideration about the types of tests that will be required — before submission.

"Devices are not drugs," he says. "Devices oftentimes cannot be blinded. Physicians know whether they've implanted a device or not. By nature, device trials have to be different from drug trials. As an industry, we don't have the greatest approach to designing and developing clinical studies. In any number of cases, the wrong clinical trial is run, which wastes a tremendous amount of time."


Government regulators should be funded by the government, not by the device industry. User fees are nothing more than a tax on innovation.

## Agency Efforts

Natasha Leskovsek, an associate at the law firm of Heller Ehrman White & McAuliffe LLP, says the user-fee law is a good way to focus the agency on better communication with device manufacturers and on providing proper guidance before the review stage.

"On the drug side, many sponsors — and rightfully so — use pre–IND, Phase II, and other meetings to make sure they and the agency are on the right path so that when it comes time to submit an application, the review team is familiar with the company's data and there will hopefully be a higher-quality application."

MDUFMA encourages more presubmission meetings, especially for expedited products. The FDA's Center for Devices and Radiological Health uses these interactions with sponsors to clarify requirements and improve the quality of applications.

"The agency is trying to put more effort into presubmission meetings to assist and give more guidance before the actual review process begins," says Ed March, senior consultant at AAC Consulting Group Inc., a subsidiary of Kendle International Inc. "The biggest problem the industry always has had is getting the guidance it needs up front. It's very tough for manufacturers to establish a path for clearance or approval unless they have consistency in guidance from the agency."

The FDA also is using a collaborative process with experts, both in and out of government, to develop clearer guidance in important and emerging new areas of device development, such as treatments for diabetes and cancer and novel drug-delivery systems and tissue therapies.

Increasingly, guidance documents have become important in the review of PMAs and 510(k)s. Even before the user-fee legislation took effect, regulatory officials began to track how many guidances they offered device manufacturers. By the end of fiscal year 2002, the Office of Device Evaluation had issued 15 final guidance documents and drafted another nine for comment.

The trade-off, though, is increased scrutiny of the application, Mr. Bent says. This is evidenced by Roche's experience.


There is already more cooperation from the FDA. Regulators are more proactive and in the device area, they are more willing to meet with companies before an application is submitted. This certainly speeds the process.

## A Different World

**The Food and Drug Administration's Center for Devices and Radiological Health (CDRH) is responsible for regulating companies that manufacture, repackage, relabel, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation emitting electronic products (medical and nonmedical) such as lasers, X-ray systems, ultrasound equipment, microwave ovens, and color televisions.**

**DEVICE CLASSES** The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act established three regulatory classes for medical devices. The three classes are based on the degree of control necessary to assure that the various types of devices are safe and effective. The most regulated devices are in Class III. Under Section 515 of the act, all devices placed into Class III are subject to premarket approval requirements. Premarket approval by the FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval.

**PREMARKET APPROVAL APPLICATION (PMA)** Similar to an approved new drug application (NDA), an approved PMA is, in effect, a private license granted to the applicant for marketing a particular medical device. Products requiring PMAs are Class III devices. They are high-risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicated through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device. The PMA is an actual approval of the device by the FDA.

**510(K)** Section 510(k) of the Food, Drug and Cosmetic Act requires those device manufacturers who must register to notify FDA, at least 90 days in advance, of their intent to market a medical device. This is known as Premarket Notification, which also is called PMN or 510(k). The FDA determines whether the device is equivalent to a device already placed into one of the three classification categories.

**MDUFMA** The Medical Device User Fee and Modernization Act of 2002 authorizes the FDA to charge a fee for medical device Premarket Notification 510(k) reviews. A small business may be eligible for a reduced fee. The law also established goals to improve the efficiency of the review process for providing and reviewing evidence on the safety and effectiveness of new medical devices.


A third party can review applications fairly quickly, saving device manufacturers a lot of time. The issue is whether the manufacturer wants to spend a few thousand dollars to save six or eight weeks of time to market.

On July 8, 2003, regulatory officials "invited" Roche to discuss the classification of AmpliChip, which enables clinical diagnostic laboratories to identify certain naturally occurring variations (called polymorphisms) in two genes, the CYP2D6 and CYP2C19, which play a major role in drug metabolism.

According to a Roche release, the company considers the AmpliChip microarray as an Analyte Specific Reagent (ASRs). Most ASRs are classified as Class I devices, exempting them from FDA premarket review requirements.

FDA officials expressed concern that the device was not properly classified as an ASR. According to a letter from regulatory officials, "The correct classification of your (Roche) device is a matter of significance, as the Act generally requires that manufacturers of Class II and Class III medical devices obtain FDA marketing clearance or approval for their products from the FDA before they can offer them for sale."

## Combination Products

Another important regulatory development was the establishment of the Office of Combination Products (OCP). In December 2002, the agency established this office to streamline the processing of complex drug-device, drug-biologic, and device-biologic combination products. The OCP is part of the Office of the Commissioner and its responsibilities cover the entire regulatory life cycle of combination products, including jurisdiction decisions as well as the timeliness and effectiveness of premarket review, and the consistency and appropriateness of postmarket regulation. The primary regulatory responsibilities for, and oversight of, specific combination products remain in one of three product centers — the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, or the Center for Devices and Radiological Health — to which the specific products are assigned.

Mr. March says this development will require the agency to have better internal communications because some of these products will require input from different parts of the FDA.

"With technological developments, we can expect more combination products coming to the agency for approval," he says. "And the review of these products will become complex."

According to Mr. Naples, the new office is a positive development because the OCP is charged with trying to define jurisdictional issues and determine which center would take the lead on a review.

Combination products also will put additional pressure on the resources at the FDA, says Amit Bohora, medical device practice leader at Frost & Sullivan.

"The pay scales at most of the government agencies are not high enough to get the best

**THIRD-PARTY REVIEW** The FDA Modernization Act of 1997 (FDAMA) allowed for third-party review of medical devices. The Accredited Persons Program was created by FDAMA, based on a FDA pilot. The purpose of the program is to improve the efficiency and timeliness of FDA's 510(k) process, the process by which most medical devices receive marketing clearance in the United States. Under the program, FDA has accredited third parties (accredited persons) who are authorized to conduct the primary review of 510(k)s for eligible devices. The accredited person conducts the primary review of the 510(k), then forwards its review, recommendation, and the 510(k) to the FDA. By law, the FDA must issue a final determination within 30 days after receiving the recommendation. In an effort to encourage greater use of the Accredited Persons Program, the FDA implemented an expansion pilot in January 2001 that allows accredited persons to review many Class II devices that were not previously eligible.

**INVESTIGATIONAL DEVICE EXEMPTION (IDE)** An IDE allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to the FDA. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.

**HUMANITARIAN DEVICE EXEMPTION (HDE)** On June 26, 1996, FDA issued a final rule to carry out provisions of the Safe Medical Devices Act of 1990 regarding humanitarian use devices (HUDs). (This regulation became effective on Oct. 24, 1996.) A HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. The regulation provides for the submission of a humanitarian device exemption (HDE) application, which is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA.

**PRODUCT DEVELOPMENT PROTOCOL (PDP)** As part of its reengineering initiative, the Food and Drug Administration, Center for Devices and Radiological Health, is proposing to implement the statutory authority for Product Development Protocol (PDP). Section 515(f) of the Food, Drug, and Cosmetic Act provides this alternative process to the premarket approval process (PMA) for Class III devices.

Source: Food and Drug Administration, Center for Devices and Radiological Health, Rockville, Md. For more information, visit fda.gov/cdrh/index.html.

and most educated employees," he says. "Reviewers of combination products have to have specific knowledge and then come up with the right review."

Michael Sweeney, general partner at the venture capital firm InterWest Partners, agrees the FDA has a tough job.

"With budget constraints, it's tough to attract the right people and keep them," he says. "People stay at the FDA for a while and then they move into industry. Historically, this has been a big problem."

## Third-Party Review

Another agency initiative has been to certify outside parties to review some of the less-complicated applications.

"The advantage is that a third-party review can be done more quickly," says Harvey Rudolph, Ph.D., global program manager for medical at Underwriters Laboratories Inc. "FDA is required to act on a third-party recommendation of substantial equivalence or not substantial equivalence in 30 days. The third party can do reviews fairly quickly and manufacturers can save a lot of time. The issue is whether to spend a few thousand dollars and save as much as six or eight weeks in time to market."

During fiscal year 2002, ODE received 127 510(k)s reviewed by third-party organizations. This was a 19% increase over the 107 submissions received in fiscal year 2001. The increase can be attributed to an expansion pilot implemented in January 2001 that permits third-party review of 510(k) submissions for a greatly expanded list of eligible devices. The pilot allows for third-party review of about 460 Class II devices for which device-specific guidance does not exist.

Dr. Rudolph says the FDA treats third parties exactly as it would treat its own reviewers.

"Our review goes to a branch chief at FDA, and we give that branch chief the same things that an internal FDA reviewer would give them: the 510(k), the check list, and a review memo that details why a product is substantially equivalent to a predicate device," he says. "The FDA has a few conflict-of-interest requirements that we must meet. Our reviewers have the same restrictions as the FDA. Reviewers can't own stock in a company, for example. They can't get involved in the development of the product."

Dr. Rudolph says his company is experiencing an increase in interest from device manufacturers in third-party review.

"In July 2003, 7% of the 510(k)s cleared by FDA were done by third parties," he says. "That's the highest it's ever been. The month before, it was about 5.5%. The average, historically, has been about 3%. We have as many 510(k)s in house this month as were approved last year."

But Mr. March says there may be a limited benefit in terms of review time by using a third-party reviewer.

"Third-party reviews may die a natural death," he says. "As the FDA becomes more efficient in terms of reviewing 510(k) submissions, the benefit derived may continue to drop."◆

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

## Experts on this topic

**STEPHEN A. BENT.** Chair of the firmwide life-sciences business team, Foley & Lardner, Washington, D.C.; Foley & Lardner is a full-service, international law firm with leading practices in intellectual property and the life sciences. For more information, visit foleylardner.com.

**AMIT BOHORA.** Medical device practice leader, Frost & Sullivan, San Antonio; Frost & Sullivan is an international marketing consulting company that monitors a comprehensive spectrum of markets for trends, market measurements, and strategies. For more information, visit frost.com.

**NEAL FEARNOT.** President, Med Institute Inc., West Lafayette, Ind.; Med Institute was established to identify and develop new medical product concepts and is a subsidiary of privately held Cook Group, a designer, manufacturer, and global distributor of minimally invasive medical-device technology for diagnostic and therapeutic procedures. For more information, visit cookgroup.com.

**MICHELLE KILE.** Partner, Intellectual Property and Life Sciences, Foley & Lardner, Washington, D.C.; Foley & Lardner is a full-service international law firm, with leading intellectual property and life-sciences practices. For more information, visit foleylardner.com.

**MARK B. LEAHEY.** Executive director, Medical Device Manufacturers Association (MDMA), Washington, D.C.; MDMA is a national trade association that represents more than 160 independent manufacturers of medical devices, diagnostic products, and healthcare information systems. For more information, visit medicaldevices.org.

**NATASHA LESKOVSEK.** Associate, Heller Ehrman White & McAuliffe LLP, Washington, D.C.; Heller Ehrman is a full-service law firm, representing a wide range of industry leaders. For more information, visit hewm.com.

**ED MARCH.** Senior consultant, AAC Consulting Group Inc., Rockville, Md.; AAC Consulting Group, a subsidiary of Kendle International Inc., is a full-service regulatory consulting firm that provides regulatory compliance and validation services to the pharmaceutical and medical-device industries. For more information, visit aacgroup.com.

**RICHARD NAPLES.** VP of regulatory submissions, reimbursement, and government affairs, Roche Diagnostics, Indianapolis; Roche Diagnostics, a division of Roche, is a leading provider of diagnostic systems and decision-oriented health information. For more information, visit roche-diagnostics.us.

**HARVEY RUDOLPH, PH.D.** Global program manager for medical, Underwriters Laboratories Inc., Bethesda, Md.; UL with headquarters in Northbrook, Ill., is an independent, nonprofit product safety testing and certification organization and a recognized third-party medical-device reviewer. For more information, visit ul.com/medical.

**MICHAEL SWEENEY.** General partner, InterWest Partners, Menlo Park, Calif.; InterWest Partners is a leading diversified venture capital firm. For more information, visit interwest.com.