BY DENISE MYSHKO

USER FEES
DEVISING A SHIFT IN POLICY

Legislation Enhances Medical Device Regulation

NEW LEGISLATION ENHANCES AND STREAMLINES THE DEVICE REVIEW PROCESS; THE GOAL IS TO MAKE REGULATORY REVIEWS MORE INTERACTIVE WITH THE REAL-WORLD AND ALLOW FOR REAL-TIME INFORMATION EXCHANGE.

The new legislation includes ways to improve the interactivity of the review process and to facilitate the exchange of more real-world, real-time information.

KIM LEVY MICROMASS COMMUNICATIONS

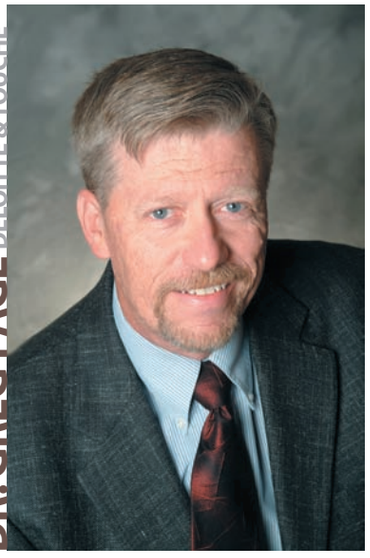
New laws and regulations aimed at improving reviews of medical devices have been put in place. In September 2007, President George W. Bush signed a broad-ranging bill that expands the regulatory authority of the Food and Drug Administration.

Combined with the legislation were several bills that had been pending for some time. Among the many components of the law were the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act (MDUFMA), which account for nearly one-quarter of the FDA's annual budget. From device manufacturers alone, the new law will enable the FDA to collect about $287 million over a five-year period.

The law enhances the device review program and streamlines the device inspection program by allowing accredited outside firms to conduct routine inspections for good manufacturing practices. The law also enhances the development of *in vitro* diagnostic devices by enabling the FDA to issue new guidances and conduct a pilot program.

In addition, the legislation changed the fee structure, as well as how the agency's performance will be measured. The fees for device submissions were reduced, but new fees were imposed for facility registration. Previously, the metrics for measuring agency performance were based on a review cycle, in other words how fast the FDA got back to the device sponsor with some sort of communication. The new piece of legislation is based on timing for final decisions.

The FDA's review of medical devices is different from its review of prescription drugs. There



DR. GREG PAGE DELOITTE & TOUCHE

On the device side, I don't think user fees have been terribly effective to date. This new proposal could change that. If regulators can meet the new timelines for turning around device reviews, user fees will be a positive.

LISA LEE MICHELS SMITH & NEPHEW

Overall, more risk assessment needs to be done to mitigate any potential adverse events related to products, especially in the pediatric population.

are three FDA regulatory classifications of medical devices. (See box on page 36 for more information.) The classifications are assigned by the risk the medical device presents to the patient and the level of regulatory control the FDA determines is needed. As the classification level increases, so too does the risk to the patient and FDA regulatory control.

"The previous user fee legislation (MDUFMA 2002) caused significant fluctuations in FDA revenue from premarket approval applications and thus it didn't quite work the way the FDA had hoped," says Kim Levy, VP of strategic planning at MicroMass Communication. "The new legislation includes ways to improve the dialogue between manufacturers and the FDA throughout the review process. There has been a huge shift in the last decade to facilitate the exchange of more real-world, real-time information as a way to take into account clinical outcomes information and risk/reward information over the course of a product's development and life cycle."

Greg Page, Ph.D., who is responsible for regulatory risk and compliance in the life sciences practice at Deloitte & Touche, says user fees are generally viewed as a positive by the pharma industry.

"But on the device side, I don't think the user fees have been terribly effective to date," he says. "The new proposal could change that. If regulators can meet the new timelines for turning around device reviews, user fees will be a positive."

Michael Sharp, Ph.D., senior VP of regulatory and clinical affairs at ConforMIS, says it's debatable whether user fees for medical devices have been beneficial.

"I think user fees have been a stealth tax on innovation," he says. "The question is: did we get what we paid for? The jury is out. I do think that MDUFMA, and similar legislation on the pharmaceutical side, is simply a way of shifting the financial support for the FDA from general tax funds to fees, which is a tax to companies. As a result, costs get passed along. In that sense, I don't think anyone should view the user fees as miraculously adding to resources at the FDA."

THE REAUTHORIZATION OF THE MEDICAL DEVICE USER FEE PROGRAM WILL PROVIDE, in addition to funds appropriated by Congress, **TOTAL REVENUE TO THE AGENCY OF $287 MILLION BY OCTOBER 2012.**

CHANGES IN THE LEGISLATION

The new law makes several changes to the medical device user fee program. Fees for submissions were reduced, but a new fee for establishment registration was implemented. The standard fee for a 510(k) premarket notification submission for the year Oct. 1, 2007, to Sept. 30, 2008, is $3,404. Companies with annual gross sales and revenue of $100 million or less, including gross sales and revenue of all affiliates, partners, and parent firms, may qualify for lower rates, amounting to $1,702, for premarket notification 510(k) submissions.

"The fees had been increasing at a reasonable clip," says Barry Sall, principal consultant at Parexel Consulting. "The new law reallocates fees in a different manner, charging less for submissions and adding the registration fee for all registered device establishments. The registration fees are about $1,706 for small companies; now every medical device manufacturer that registers with FDA needs to pay a user fee, whether a company makes 20 submissions, one submission a year, or zero submissions a year."

Lisa Lee Michels, group director of regulatory affairs at Smith & Nephew, says the reduction of the fees will help companies and is likely to be a cost savings.

"The benefit of the reauthorization of fees is that the legislation strikes a fair balance for both industry and the FDA," she says. "From an industry standpoint, user fees have been reduced and there is now standardization. This provides the FDA with adequate resources to complete the reviews on time, based on its goals and objectives for the review cycles."

Andre' DiMino, co-CEO and vice chairman of Ivivi Technologies, says the reduced fees specifically help smaller companies.

"I strongly believe that small companies are where innovation comes from, and high fees can impact that innovation," he says. "Reducing the fees for smaller companies is a welcome relief."

The new law also changed how the agency's performance is assessed related to the review of medical devices. Previously, the performance metrics were based on a review cycle. Now they are based on time for final decisions.

"For a 510(k) submission, the new legislation requires that the FDA renders a final decision on 90% of applications in 90 days, which is relatively fast for what may be very complex submissions," says John Smith, M.D., J.D., a partner at Hogan & Hartson. "Companies need to ensure that their 510(k) applications are as complete as possible given this new emphasis on speedy final decisions. At this point, it's unclear how the agency is going to

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handle routine situations where an application needs additional information under this new paradigm, although the agency has recently placed more emphasis on interactive review."

He says before the implementation of user fees and associated performance standards under MDUFMA, the agency was often willing to keep applications open for long periods of time because there was less pressure to close out a file.

"Under MDUFMA, the agency has largely limited 510(k) reviews to two sets of questions following the original submission," Dr. Smith says. "The first review addressed any questions that the agency had on the original submission. If there were still open questions after the company answered the first round of questions, the FDA would once again request additional information. If this second response still left open questions, it has largely been agency policy to find the device not substantially equivalent."

Dr. Smith says while the 2007 legislation encourages more open and ongoing communications with sponsors, it also creates challenges.

"The downside is that the agency has to meet even tighter performance goals," he says. "With limited flexibility, there's the possibility that the agency could have difficulty dealing with problem 510(k) submissions since the deadlines are relatively tight."

FDA officials say they have made significant progress toward meeting the fundamental objectives of MDUFMA. The user fees provided by MDUFMA and the annual appropriations have allowed the agency to make significant improvements in the device review program.

The agency has hired medical specialists, statisticians, software experts, and engineers. It has increased the use of outside experts, particularly for novel technologies; and it has made improvements to the IT systems, such as enhanced tracking of applications and reporting systems.

According to FDA officials, the agency's overall performance to date for fiscal year 2003 through fiscal year 2006 receipt cohorts is consistent with the expectations for the device review program. Of the 50 performance goals that were in effect during this period, the FDA's performance to date includes meeting or exceeding 32 goals and not meeting six goals.

FIRST-OF-ITS-KIND FOUNDATION TO HELP THE FDA MEET ITS GOALS

The Reagan-Udall Foundation was established as part of the Food and Drug Administration Amendments Act of 2007, which was ratified in September 2007. The foundation is an independent, nonprofit organization created to advance the FDA's mission to modernize the development of products regulated by the agency.

The statute calls for a diverse 14-member board: four representatives from the general pharmaceutical, device, food, cosmetic, and biotechnology industries; three representatives from academic research organizations; two representatives from patient or consumer advocacy groups; one member representing healthcare providers; and four at-large representatives with expertise or experience relevant to the purpose of the Reagan-Udall Foundation.

The foundation is charged with identifying unmet scientific needs in the development, manufacture, and evaluation of the safety and effectiveness of FDA regulated products, including postmarket evaluation and to establish scientific projects and programs to address those needs. The foundation will be an important vehicle to address the priorities and opportunities identified in the FDA's Critical Path reports and to help modernize the product evaluation sciences.

The agency is to establish an education and training program as part of this foundation and a fellowship to bring in scientists from all of the new scientific fields into the FDA, as well as train FDA scientists in advanced scientific disciplines.

Source: Food and Drug Administration, Rockville, Md. For more information, visit fda.gov.

DR. MICHAEL SHARP CONFORMIS

The FDA implemented a new goal for fiscal year 2007: 50% of premarket approvals (PMA)/panel-track PMA supplements received are to have an FDA decision within 180 days. Twenty-five goals had higher performance levels for fiscal year 2007.

CLINICAL-TRIAL DATA

The new law also expands the existing government database on clinical trials to include clinical-trial registry information on new medications and devices. The law requires that trials for drugs and devices that are beyond Phase I be registered. Sponsors also will be required to post basic trial results on the database for approved drugs and devices.

FDA officials say database requirements could be further expanded to include adverse event information and even potentially trials of unapproved products.

"The FDA Amendments Act, for the first time, requires device manufacturers to provide information on all clinical trials for the registry database as has previously been required of drugs and biologics," Ms. Levy says. "There are some exclusions, for example feasibility studies. But for clinical studies that involve the testing of a device intervention versus a control group that information has to be reported."

While the pharmaceutical industry has had to report trial data for some time now, this is a new requirement for device manufacturers.

"There are different concerns in the device industry," Mr. Sall says. "On the device side, information that is part of the submission can

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With the new legislation, the paradigm for assessing FDA performance has shifted from a review cycle-based performance metric to a final decision-based metric.

ANDRE' DIMINO IVIVI TECHNOLOGIES

Safety and controls are important and it's good to have a level playing field. It's also important not to overregulate and drive innovation out of the country.

remain confidential until after the device is approved or cleared. Keep in mind, about 85% to 90% of all the new medical devices that come onto the market in a given year have no clinical data supporting them. Data simply aren't required for most Class I and Class II devices. This new requirement won't have a blanket effect industrywide. For some companies it will be a substantial change that they will have to accommodate in their plans; others simply won't notice it."

Some industry experts question the benefits of reporting clinical-trial data early on.

"Some believe that the disclosure of clinical-trial data before FDA clearance or approval will let the competition know about the product development process too soon," says Peter Scott, VP of quality assurance and regulatory affairs at Immunicon. "Some device trials take a couple of years to complete, with additional time needed for the FDA review process. So the provision that information is posted only after clearance or approval will be important."

Dr. Page stresses that clinical data often are subject to interpretation.

"The downside to allowing the public to view raw clinical data is that it could possibly lead to more litigation," he says. "Conceptually, I like the idea of raw data being available to the public, as long as the information is being evaluated by qualified people in a scientifically valid and medically valid environment. But there is the potential that data could be misused to support what may be frivolous claims against drug and device manufacturers."

PEDIATRIC PROVISIONS

The new law also has sections that increase the FDA's responsibilities around protecting and enhancing the health of children: The Pediatric Research Equity Act, The Pediatric Medical Device Safety and Improvement Act, and The Best Pharmaceuticals for Children Act.

In the medical-device provision, the law requires that certain device applications include a description of pediatric populations.

DEVICE CLASSIFICATIONS

The Food and Drug Administration has established classifications for about 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels.

Each of these generic types of devices is assigned to one of three regulatory classes — Class I, Class II, and Class III — based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements that apply to them are:

Class I — Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments. Most Class I devices are exempt from the premarket notification and/or good manufacturing practices regulation.

Class II — Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes. Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. Special controls may include special labeling requirements, mandatory performance standards, and postmarket surveillance.

Class III — Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. This is the most stringent regulatory category for devices. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or that present a potential, unreasonable risk of illness or injury.

Premarket approval is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Not all Class III devices require an approved premarket approval application to be marketed.

Class III devices that require a premarket approval include replacement heart valves, silicone gel-filled breast implants, and implanted cerebella stimulators.

Source: Food and Drug Administration, Rockville, Md. For more information, visit fda.gov.

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Before the user fee program, review times for medical devices were getting longer. In some respects, review times have stabilized and have even been reduced.

It also calls for the FDA to track and report to Congress the number and types of devices that are approved specifically for children or for pediatric conditions.

Meeting the requirements of this part of the legislation could be challenging, Mr. Sall says.

"The equation is different for many devices than for pharmaceuticals," he says. "For a pharmaceutical product, the dosage may have to be adjusted a bit for pediatric administration, but fundamentally there is no change to the product or the manufacturing methodology. But for many devices, if they were originally designed for adult use, changing them for application in a pediatric setting is quite different. For example, the device would have to be sized smaller. There may be other considerations, such as making sure the device can accommodate the growth of the patient over time."

The FDA also has been required to establish a third-party inspection program. Agency officials say this may be particularly useful to

BARRY SALL, PAREXEL CONSULTING

U.S. firms that compete in international markets and face multiple sets of regulatory requirements. A single third-party inspection may satisfy both U.S. and foreign requirements as well as meet International Organization for Standardization (ISO) or other international standards requirements.

Dr. Page says this provision of the new requirement is not as effective as it could be.

"The legislation is trying to revamp or improve upon the third-party inspection program," he says. "On the device side, for the last several years the agency has had a system in place that allows, in essence, for independent contractors to act as third-party inspectors representing the FDA. The idea was that companies would be prepped for real FDA inspections but I don't think there is an effective substitute for an FDA inspection." ✦

PETER SCOTT, IMMUNICON

Many companies believe that the disclosure of clinical-trial data before FDA clearance or approval will let the competition know about the product development process too soon.

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

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