

THE FDA'S BALANCING ACT:

Approve devices too slowly and lives could be lost during the wait // too quickly, and flaws might slip through undetected // so where's the **happy medium?**

Dangerous Devices

■ BY ANITA SLOMSKI // ILLUSTRATIONS BY HARRY CAMPBELL

Joshua Oukrop's cardiologists were stunned when the 21-year-old college student died from sudden cardiac arrest during a biking trip near Moab, Utah, in 2005. But they might have been less surprised had they known the history of the device—a Ventak Prizm 2 DR implantable cardioverter defibrillator, manufactured by Guidant Corp.—placed in Oukrop's chest to correct abnormal heart rhythms associated with a condition called hypertrophic cardiomyopathy. Guidant, now part of Boston Scientific, had received more than two dozen reports of the device's failing to deliver a life-saving jolt to hearts that sometimes quiver instead of beat.

In 2002, just months after Oukrop's implant, Guidant twice modified the device to prevent short circuits, and the company says that in 2003 it notified the U.S. Food and Drug Administration about the design changes. But according to the U.S. Justice Department, which filed criminal charges against Guidant last February, the company failed to include a required disclosure—that the device had been altered to correct a safety flaw. Meanwhile, physicians had implanted 24,000 Prizm ICDs, which were finally recalled a few months after Oukrop's death. In April, Guidant pleaded guilty to withholding information from the FDA.

The story is one among many describing fatal consequences of faulty medical devices. In 2006, the most recent year for which statistics have been compiled, the Center for Devices and Radiological Health—the FDA division whose mission is to ensure the safety and effectiveness of about 100,000 types

of medical devices—received 224,197 reports of faulty products, including 116,086 device-caused injuries and 2,830 deaths. Many consumer groups and physicians think that, too often, the CDRH approves devices without rigorous clinical evidence that a product works and is safe, and that the agency is remiss in monitoring devices already on the market.

“The FDA's standards for medical devices are much too lax,” says Mitchell Feldman, a professor of medicine at the University of California, San Francisco, School of Medicine. As a consultant to the California Technology Assessment Forum, an independent nonprofit organization that evaluates new medical technology, Feldman reviews the clinical evidence supporting device manufacturers' claims of safety and effectiveness. The CTAF sets its bar high: Only a quarter of CDRH-approved new technologies pass muster.

While many people assume that the FDA scrutinizes medical devices as carefully as it does prescription drugs, the rules for devices and drugs are different, according to epidemiologist Diana Zuckerman, president of the National Research Center for Women & Families, which studies health programs, policies and agencies. “For the riskiest devices, the FDA requires ‘reasonable assurance of safety and effectiveness,’ but drugs have to be ‘proven safe and effective,’” Zuckerman says.

There are good reasons that testing differs for the two kinds of medical products—you wouldn't implant a placebo pacemaker in a patient's chest—and some experts maintain that problems with and recalls of medical devices have more to do with the devices' increasing complexity than with the CDRH's failure to reject unsound technology. “We may need more post-

market surveillance,” says John Somberg, a professor of pharmacology and medicine at Rush University Medical Center in Chicago, who consults with the CDRH on cardiac and renal devices. “But that isn’t an indictment of the device approval process. If we change the initial approval process, we’ll have to stick with older devices—and that will harm patients.”

The agency has acknowledged that it needs to change its standards and processes, with preliminary rule changes this summer and an overhaul in 2011. Meanwhile, though, device-makers worry that the CDRH, in tightening its regulations, will reject too much new technology. Will the CDRH be able to strike the right balance between manufacturers’ call for a less burdensome process and the public’s insistence that the CDRH protect patients from risky devices?

FDA regulation of medical devices began only in 1976, after a debacle involving the Dalkon Shield, an intra-uterine contraceptive device notorious for causing deadly infections, helped spur Congress to pass the Medical Device Amendments to the Food, Drug and Cosmetic Act of 1938. The new law required testing and approval before a device could be marketed.

But the FDA couldn’t evaluate all the devices on the market. Instead, the legislation called for the agency to slot each device into one of three classes and to undertake a thorough review only of class III devices—the most potentially dangerous. The others, in classes I and II, were assumed to be safe and effective. Moreover, though all new devices would be subject to FDA approval, if a manufacturer could demonstrate that a new product was “substantially equivalent” to an existing class I or class II device—with the same intended use and technological characteristics—approval might be hastened.

This faster process, known as the premarket notification program, or 510(k)—it was named after a section of device law—primarily ensures that a device meets standards for

labeling, design and performance. And for many class I and class II devices, that approach makes sense. Most in class I—tongue depressors, hearing aids and forceps, for example—pose little risk and are approved with minimal scrutiny. Class II devices—including contact lens solutions, motorized wheelchairs and electric bone drills—are more complicated and so are evaluated more carefully. But the CDRH approves most of them.

The CDRH reserves its most stringent controls for class III devices—those that are implanted, are life-sustaining or pose “potential unreasonable risk of illness or injury.” Devices engineered with breakthrough technologies also fall into class III, as do pacemakers, breast implants, cochlear implants and artificial joints. They undergo a full review called premarket approval, which takes at least a year, compared with a minimum of three months for a 510(k) review. Manufacturers must submit clinical data, the CDRH can inspect manufacturing facilities, and the agency may require post-market studies. The CDRH can subject 510(k) reviews to the same steps, and a 510(k) review could take as long as a PMA if the data required are complex.



The 1976 legislation presumed that eventually every new class III device would be subject to full PMA review. But according to a 2009 Government Accountability Office report, 21% of the 1,062 class III devices the CDRH approved from 2003 through 2007 underwent the 510(k) process.

Manufacturers have no desire to see more devices go through the PMA process, which is time-consuming and expensive. In addition to study costs, there are CDRH fees, which in 2005 averaged \$200,725. (In contrast, getting 510(k) clearance cost just \$3,693, on average.) But money isn't the only issue. "If we didn't have the 510(k) process, the flow of new treatments would be reduced to a trickle. That wouldn't be good for patients or the industry," says David Nexon, senior executive vice president for policy at AdvaMed, the trade organization for the \$123 billion medical device industry. "The FDA clears only 30 to 40 new drugs a year. If every device had to meet a PMA standard, which is equivalent to drug approval, the CDRH would be overwhelmed."

However, some devices that came to market via the 510(k) process have had dangerous flaws. Bausch & Lomb's ReNu with MoistureLoc contact lens solution exposed users to a fungus that caused eye infections so severe that some patients needed corneal transplants, says the National Research Center's Zuckerman. She also cites Boston Scientific's ProteGen bladder sling for stress incontinence, which caused vaginal erosion, and Vitek jaw implants, which shed particles, causing bone degeneration in the jaw and skull.

Even within the FDA, the 510(k) process has come under fire. A group of FDA scientists wrote to Congress in the fall of 2008 and to the new Obama White House in early 2009, complaining that CDRH managers have "ordered, intimidated and coerced FDA experts to modify their scientific reviews, conclusions and recommendations."

The approval of Menaflex, ReGen Biologics' collagen scaffold for knee repair, came after the scientists' letter but illustrates the problems they cited. ReGen says Menaflex can regenerate torn knee cartilage and that it is similar to an approved shoulder implant and to a surgical mesh for hernia repair. But FDA scientists twice rejected the company's 510(k) application, saying that Menaflex is a novel device and that they needed proof it could withstand the load on knees.

ReGen asked members of Congress from the company's home state to intervene. After the FDA rejected ReGen's third application, the then head of the CDRH convened a panel of outside physicians—chosen with ReGen's input—to determine whether the device was equivalent to marketed implants. Despite reservations from even some of those experts and a key FDA scientist, Menaflex was cleared for marketing in December 2008.

A subsequent investigation, ordered by Congress, found that the CDRH had deviated from established procedures and practices and compromised the "integrity of the review." (A separate investigation by the U.S. Department of Health and Human Services found no evidence of criminal wrongdoing, however.) The report, issued in September 2009, called for the CDRH to re-evaluate Menaflex.

The CDRH agreed, and announced that it would convene a working group to evaluate all 510(k) decision-making. The FDA also commissioned a \$1.3 million Institute of Medicine

"The FDA clears only 30 to 40 new drugs a year. If every drug had to meet a PMA standard, which is equivalent to drug approval, the CDRH would be overwhelmed."

study to determine whether the 510(k) process protects patients and promotes innovation—and what should be changed if it doesn't. The study is expected to be completed in 2011. (In the meantime, although the Centers for Medicare & Medicaid Services have decided not to cover Menaflex implants, they have not been found to be harmful.)

For the comparatively few devices going through the full PMA process, the CDRH outlines the types and amount of clinical evidence it expects, then meets with the manufacturer to determine a study's design, size and duration. Though human clinical trials are usually required, the agency may accept other sources of "valid scientific evidence," including engineering analyses, animal studies,

laboratory tests, computer simulations, case histories and “robust human experience.”

Compared with the drug approval process—animal studies followed by three phases of human clinical testing—the PMA process may seem abbreviated. According to a paper published in the *Journal of the American Medical Association* in late 2009, 65% of PMAs for high-risk cardiovascular devices approved between 2000 and 2007 were based on single human studies. Subjects chosen for the research were also questionable, says Rita Redberg, director of Women’s Cardiovascular Services at the University of California, San Francisco, Medical Center and an author of the *JAMA* study. “The patient population

Out of Bounds //

Physicians can use medical devices “off label,” but manufacturers can’t promote those uses.

The Food and Drug Administration doesn’t regulate how physicians practice, so physicians are free to use medical devices for purposes other than those for which the technology was approved. Indeed, such off-label applications are common. The first metal stents, approved by the FDA to hold open bile ducts obstructed by tumors or inflammation, soon found a far more widespread use—keeping coronary arteries from collapsing after balloon angioplasty. But the FDA draws the line at marketing medical devices for nonapproved uses.

Manufacturers who suggest to physicians and hospitals that their products have additional, if unsanctioned, uses can find themselves in serious trouble—even when the application has been broadly accepted by the medical community. In February, for example, the U.S. Justice Department announced that devicemaker AtriCure had agreed to pay \$3.76 million to resolve allegations that it had promoted its surgical ablation devices, which use radio frequency waves to stop a wound from bleeding, as a treatment for the abnormal heart rhythm atrial fibrillation. That fine comes even though cardiologists have employed such devices for that purpose for 20 years. Another maker of ablation devices, Estech, paid \$1.4 million in a settlement after similar allegations, and in April the agency issued a warning letter to St. Jude Medical that its marketing materials promoting an ablation device to treat AF were in violation of the law.

That’s not just bureaucratic foot-dragging, says Mitchell W. Krucoff, co-director of the Cardiovascular Devices Unit at the Duke Clinical Research Institute. “If a device is used in patient populations that haven’t been studied, unexpected things can happen,” Krucoff says. And while surgical ablation devices enjoy a thriving off-label market, evidence of safety and efficacy is lacking. “At present very limited data establishing the long-term impact of catheter or surgical AF ablation on major morbidity and mortality are available,” says a consensus statement from the Heart Rhythm Society.

often excluded people with diseases other than the one treated by the device, and 67% were men, though half of those with heart disease are women,” she says.

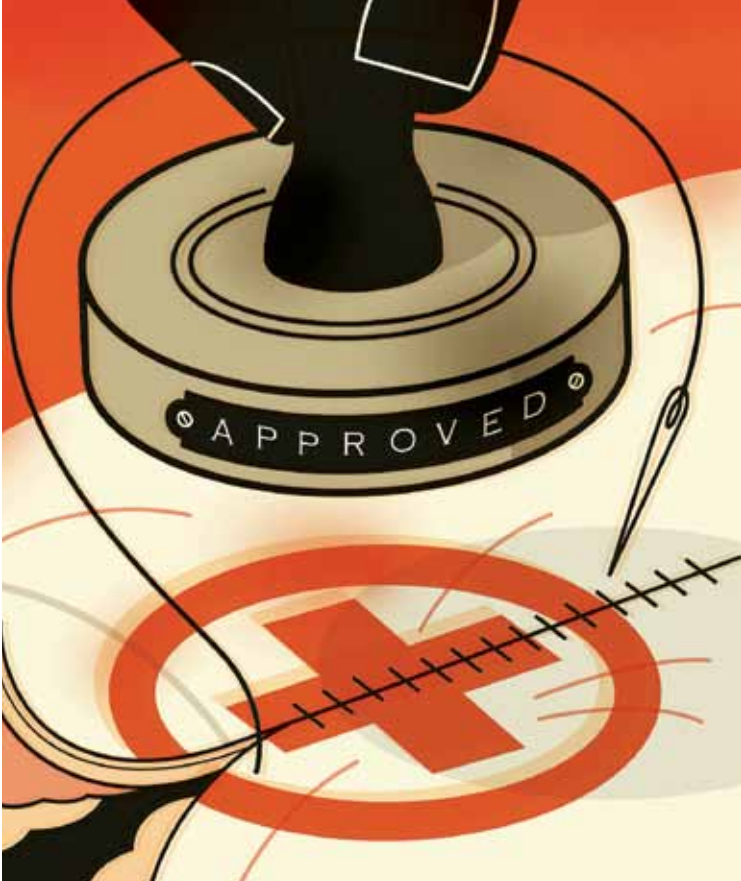
The FDA criticized Redberg’s analysis for depending on CDRH summaries of PMAs (rather than the complete evidence included in applications) and for choosing less-than-ideal metrics. But this year, the FDA collaborated with Harvard scientists to publish a study of cardiovascular device PMAs finding that information about participants was incomplete and that indicators of safety and effectiveness were not always clearly defined. The study, says Bram D. Zuckerman, director of the FDA Division of Cardiovascular Devices, has prompted the FDA to more carefully screen the quality of clinical trials and to increase the representation of women and minorities.

“For surgical implants, the bar is still very low regarding the evidence the FDA will accept,” says Richard A. Deyo, a professor of evidence-based medicine at Oregon Health and Science University. For example, in approving a metal prosthesis used in hip resurfacing, the CDRH relied on case reports from the surgeon who had developed the resurfacing technique, a shortcut the UCSF’s Feldman considers a mistake. “Of course he’s going to have the best results,” Feldman asserts.

Yet the notion that device testing should mirror the extensive process for new drugs raises issues of time, money, practicality and even necessity. “Doing a major operation to implant a device is obviously more expensive than giving someone a pill,” Deyo says. “And while drug trials often use placebos, sham operations may be unfeasible.”

Moreover, because devices may be superseded by new technology within a few years—compared with drugs that can be around for decades—there’s a tendency to think that device testing needn’t involve human trials as large as those that would be required for drugs. “That’s not an argument for putting an unsafe device on the market,” says Rush University’s Somberg. “But you must have a streamlined process that allows manufacturers to test the smallest numbers of patients that will reveal safety and effectiveness issues.”

Consider too that, though medical devices may prove deadly, they normally affect only a discrete part of the body. “When you’re evaluating a pharmaceutical product, you have to establish dosing and look for unanticipated adverse events in the rest of the body,” says Christy Foreman, acting director of the CDRH’s Office of Device Evaluation. “With medical devices, one well-designed study coupled with extensive bench testing



will sometimes give us all we need. Testing an orthopedic implant in the lab for metal fatigue will provide more information about that implant than a clinical trial ever could.”

Whatever scrutiny medical devices receive before they’re marketed, some will inevitably reveal shortcomings only after they’re widely used, so post-market surveillance is crucial. A significant number of products are pulled from the market each year. In 2006 the CDRH initiated recalls of 1,550 products. Twenty-one recalls came with the most urgent warning that using the device would likely “cause serious health problems or death.”

Yet in its post-market monitoring, the CDRH relies mostly on manufacturers to report problems. One way to supplement that self-policing, policy experts suggest, would be for the CDRH to mine insurance claims data. That might help identify which devices are consistently creating problems. However, insurance carriers would first need a system to code the make and the model of every device in a patient’s record.

The CDRH could also consider results of independent testing. The CTAF, for example, invites manufacturers, physicians and insurance companies to debate the safety and effectiveness of new devices, and then pays internists with academic appointments to evaluate the clinical evidence supporting a device’s safety and effectiveness. Based on those reviews, a panel of experts votes on whether the device meets five criteria for safety and effectiveness.

The beleaguered CDRH has announced several initiatives to improve its track record on both initial approvals and post-market monitoring. In April the agency said it was creating a Website to post summaries of its reviews of the data that device manufacturers submit, performance details on approved devices, and actions the CDRH is taking to respond to problems. The agency also disclosed that it was changing the way its expert panels review and vote on device applications to allow more open, in-depth discussion. In addition, the agency put manufacturers on notice that increased design and engineering information will now be required for reviews of infusion pumps, a technology that has had persistent problems.

This summer the CDRH also expects to make some “obvious changes” to the current 510(k) process. “But we won’t make large-scale changes until we see the Institute of Medicine report next year,” Foreman says. In the meantime, the CDRH will continue assessing its requirements for clinical studies to make them “more robust,” she adds. “We want the flexibility to bolster our review as device technology evolves.”

“There’s a lot of room for the FDA to get better,” says Mitchell W. Krucoff, a co-director of the Cardiovascular Devices Unit at the Duke Clinical Research Institute. “But Congress needs to give the FDA the resources to hire enough people to do the job. You need an economy that will support federal agencies and a political process that won’t tear them apart because they are perceived as big government. The FDA will be the first to say it wants, and needs, to do better.” ■

→ DOSSIER

1. “*Semper Fidelis—Consumer Protection for Patients With Implanted Medical Devices*,” by William H. Maisel, *The New England Journal of Medicine*, March 6, 2008. Maisel describes how the FDA’s regulation of devices allows manufacturers to knowingly sell potentially defective devices while they seek approval of a new design to fix the defects.
2. “*Postmarket Evaluation of Breakthrough Technologies*,” by Sunil V. Rao et al., *American Heart Journal*, August 2008. The American College of Cardiology and the Duke Clinical Research Institute convened experts to address shortcomings in post-market surveillance of medical devices. Among the recommendations: to enroll sicker patients with complex diseases in studies to obtain more realistic data on device safety.
3. *Hope or Hype: The Obsession With Medical Advances and the High Cost of False Promises*, by Richard A. Deyo and Donald L. Patrick (AMACOM, 2005). The authors argue that the user fees the FDA charges device manufacturers to review products keep the agency beholden to corporate interests. They suggest alternative approaches such as an independent safety board.