

Medical Device Regulation: An Introduction for the Practicing Physician

William H. Maisel, MD, MPH

Patient care for the practicing physician increasingly relies on medical devices. The U.S. Food and Drug Administration is responsible for the safety and effectiveness of medical devices in the United States. In addition to playing a role in the clinical use of devices, physicians may also participate in their design, production, use, and safety by expressing their need for certain products, by providing practical input and feedback into product design, by participating in device-related research, and by reporting

device-related adverse events. Physicians should understand the rules that govern the approved and unapproved use of medical devices as well as device premarket evaluation and approval processes and device postmarket surveillance.

Ann Intern Med. 2004;140:296-302.

For author affiliation, see end of text.

www.annals.org

The past decade has witnessed an explosion in the variety, use, and complexity of medical devices. The U.S. Food and Drug Administration (FDA) is charged with ensuring the safety and effectiveness of medical devices in the United States and regulates more than 1700 types of devices, 500 000 medical device models, and 23 000 manufacturers (1–5).

The term *medical device* is defined by the U.S. Congress as (6) “an instrument . . . which is . . . intended for use in the diagnosis, . . . the cure, . . . treatment, or prevention of disease . . . and which does not achieve any of its intended purposes through chemical action within or on the body . . .” This definition creates a distinction between medical devices and drugs (1). Products that are a combination of drug and device are generally regulated within the FDA on the basis of the mechanism of principal action, as determined by the FDA (1). For example, both drug-eluting coronary stents and bone cement that contains antibiotics are regulated as medical devices.

Medical devices vary greatly in complexity, ranging from implantable life-sustaining devices, such as pacemakers and defibrillators, to less sophisticated “devices,” such as bedpans and gloves (2). Some human tissues, including heart valve allografts, are regulated as devices, as are many device accessories, such as plastic tubing and computer software (2, 7). Overall, more than 4% of the noninstitutionalized U.S. population has at least one implanted medical device, and some form of medical device is used for almost every patient (8). The total global medical device industry is a \$130 billion business, and almost half of the global production and consumption occurs in the United States alone (1).

Patient care increasingly relies on medical devices (9). In addition, many patient–consumers use the Internet to learn about new medical devices and emerging technologies, some of which may not yet be approved for use in the United States (10). Physicians play a role in not only the clinical use of a device but also at times device design, production, use, and safety by expressing their need for certain products, by providing practical input and feedback into product design, by participating in device-related re-

search, and by reporting device-related adverse events (11). Physicians should understand the rules that govern the approved and unapproved use of medical devices, device premarket evaluation and approval processes, and device postmarket surveillance.

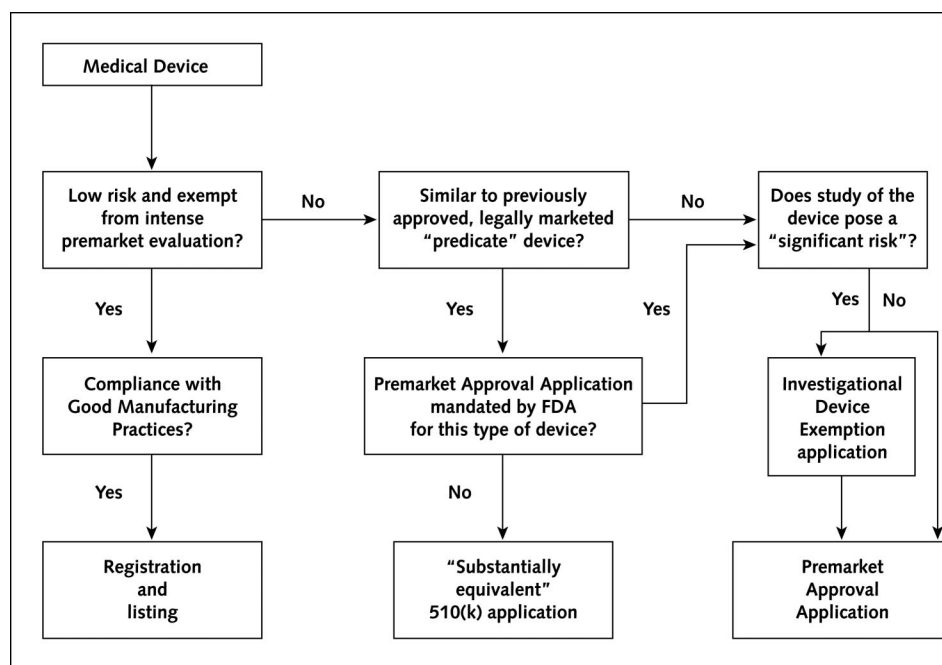
PREMARKET EVALUATION AND APPROVAL PROCESS

By the late 1960s, more than 1000 manufacturers of medical devices shipped products with a total value exceeding \$1 billion (7). In the early 1970s, a government report documented more than 10 000 injuries resulting from medical devices (1, 12), and a short time later, the Dalkon Shield intrauterine device (A.H. Robins Co., Richmond, Virginia) was withdrawn from the market after more than 200 second-trimester septic abortions and 11 maternal deaths (4, 13).

In response to these and other events, Congress enacted the Medical Device Amendments of 1976 to better allow the FDA to establish the safety and effectiveness of medical devices (7, 14). The legislation was based on the idea that the degree of device regulation should correlate with the degree of risk posed by the device. Therefore, FDA premarket evaluation and approval, conducted by the Center for Devices and Radiologic Health (CDRH) (4, 7), depend on the complexity of the device and the perceived risk to the patient.

Three regulatory classes (I, II, and III) were defined by the legislation (7, 15, 16). All devices are subject to “general controls” including proper labeling and adherence to predefined Good Manufacturing Practices, such as a demonstration of adequate packaging and storage (7, 15). Class I devices are low-risk devices. They have minimal potential for harm and include such items as stethoscopes and tongue blades (15, 16). Their safety and effectiveness are reasonably assured by the general controls (7, 15, 16). Class II devices are moderate-risk devices. General controls alone are deemed insufficient to ensure their safety and effectiveness (7, 16). These devices, which include a broad range of products, such as computed tomography scanners and gastroenterology endoscopes, must meet or exceed cer-

Figure. Overview of the medical device approval process.



Some medical devices are perceived to be low risk and are exempt from close scrutiny by the U.S. Food and Drug Administration (FDA). In some cases, the device's manufacturer need only demonstrate compliance with Good Manufacturing Practices and then register and list the device with the FDA. Medium-risk devices that have the same intended use and same technological characteristics as a previously approved, legally marketed product are considered "substantially equivalent" to this "predicate" device and may be evaluated with a 510(k) application. This application requires demonstration that the predicate device is safe and effective and that the new device raises no new questions of safety or effectiveness. The FDA mandates the more comprehensive Premarket Approval Application for certain higher-risk devices or devices that raise new questions of safety or effectiveness. Investigational devices undergoing clinical study require an Investigational Device Exemption if they potentially pose a "significant risk" to the patient.

tain predefined product performance standards (7). Products categorized as class III are perceived to be higher-risk devices, such as pacemakers and silicone breast implants. Their safety and effectiveness can be ensured only by a thorough premarket evaluation and approval process (7, 16).

Before receiving FDA approval to market a new medical device in the United States, manufacturers must demonstrate that the device is safe (its benefits outweigh the risks) and effective (it reliably does what it is intended to do) (3, 4). Data to support safety and effectiveness may include device design verification and validation studies, observational studies, randomized clinical trials, epidemiology studies, animal studies, bench research, engineering or manufacturing tests, and statistical risk analyses. The specific data required by the FDA to determine safety and effectiveness depend on the type of device, its intended use, and the perceived risk to the patient's well-being. A device designed to treat a life-threatening condition for which no alternative therapy exists may have a higher acceptable risk than a device designed to treat a benign condition. The FDA is required by Congress to use the "least burdensome" approach, meaning that manufacturers are required to provide only data that are necessary to demonstrate safety and effectiveness (17).

Most devices enter the market in 1 of 2 ways (3): by demonstration of "substantial equivalence" to a previously

approved, legally marketed device or by demonstration of safety and effectiveness through a Premarket Approval Application. The remaining lower-risk devices, such as elastic bandages and otoscopes, are exempt from this intense scrutiny and may need to undergo only "registration and listing" with the FDA or may require only evidence of compliance with manufacturing guidelines (for example, products requiring sterility) (1, 18) (Figure). "Guidance documents," which are written by the FDA, aid manufacturers by summarizing FDA expectations about the amount and type of data that will be expected before approval of a specific type of device (19).

"Substantial equivalence" requires demonstration that the new medical device is similar to a legally marketed, "predicate" device with regard to intended use and technical characteristics (7, 15). Applications of substantial equivalence are called "510(k) applications" on the basis of the title and section of the 1976 Medical Device Amendments that established them (15). However, devices with different or new technological characteristics may still claim substantial equivalence if the predicate device has been documented to be safe and effective and the new device raises no new important questions of safety or effectiveness. For example, when a company marketing endoscopes (laparoscopes, laryngoscopes, and cystoscopes) made a small change to the optical system of the scopes, the FDA

agreed that the design, materials, and function of the scopes were similar to those of the previous generation of scopes and granted approval without additional clinical data (20).

The second route to market for a medical device is through the Premarket Approval Application process. This process involves analysis of information about product safety and effectiveness, often in the form of clinical data (15). Design and manufacturing information as well as nonclinical laboratory testing (for example, studies related to shelf life or biocompatibility) are also part of the application (3). The specific data required depend on the device. For example, before approving biventricular pacemakers and implantable cardioverter defibrillators capable of delivering cardiac resynchronization therapy to treat heart failure, the FDA required a randomized, multicenter clinical trial involving hundreds of patients (21). Approval of a glucose watch (noninvasive monitoring of blood glucose level), on the other hand, did not require data from a formal randomized clinical trial (22). However, data were presented on the accuracy of the device during *in vitro* glucose measurements and in the presence of potential “interfering” medications in various environments (that is, different temperatures, humidities, and altitudes); these data were then compared with simultaneous actual blood glucose measurements in humans (22).

When a device that requires a Premarket Approval Application is ready for clinical testing, the FDA issues an Investigational Device Exemption to the manufacturer. This exemption grants permission to use the device in humans in an experimental situation to assess its safety and effectiveness (3, 15, 23). An Investigational Device Exemption can be used only at a specific institution after approval by the institution’s institutional review board (15). Violations of federal regulations during use of an investigational device under an Investigational Device Exemption could result in disqualification of investigators, institutional review boards, and institutions from current or future research (24).

The FDA annually receives approximately 4000 510(k) applications claiming substantial equivalence compared with fewer than 100 Premarket Approval Applications (3, 25). To a manufacturer, the advantage of a 510(k) application is that it is generally faster and less expensive than its Premarket Approval Application counterpart (4). To the FDA, a 510(k) application requires fewer resources than does a Premarket Approval Application and allows the FDA to handle its large workload by requiring less of the manufacturers. The FDA tries to balance the drawbacks of this approach, that is, fewer data about the safety and effectiveness of the device in question, by requiring Premarket Approval Applications for selected devices that they deem to be high risk (1, 7). On occasion, formal FDA Medical Device Advisory Panels are convened to make recommendations on device approval or the need for additional data (26). Because of the variety of medical devices

and the expertise required to evaluate a given device, physicians, scientists, industry, and patient representatives all participate in the FDA Medical Device Advisory Panel process (7).

During the premarket evaluation phase, the ability of the FDA to identify and predict which products will prove harmful may be limited. Rare events or complications that require years to develop may not be appreciated. Even evaluation of devices undergoing clinical trials is limited by the relatively small size and short duration of the studies. Longer, larger clinical trials increase both the cost of product development and the product-to-market time. The challenge to the FDA is to keep product-to-market time short to allow patients to benefit from medical advances while continuing to ensure the safety of those who enjoy the product’s benefits (27). In some cases, the FDA shifts some product evaluation from the premarket phase to the postmarket period, thereby allowing a device to reach the market sooner (28). This creates the potential for a large number of patients to be rapidly exposed to a newly approved product in the absence of long-term follow-up data and highlights the need for selected ongoing postmarket evaluation.

POSTMARKET EVALUATION

During the 1980s, device manufacturers were criticized for inadequately reporting adverse events to the FDA and failing to conduct appropriate product recalls (7). In 1986, the withdrawal of a mechanical heart valve from the market because of premature strut failure affected more than 400 patients and was cited as additional evidence of inadequate postmarket surveillance (3, 29). In response, Congress enacted the Safe Medical Devices Act of 1990 and Medical Device Amendments of 1992 (4, 30), which strengthened postmarket surveillance by requiring health care facilities to report serious device-related injuries or deaths, by establishing tracking of certain high-risk devices, and by giving the FDA authority to require tracking for any other device (7).

The goal of postmarket surveillance is to “enhance the public health by reducing the incidence of medical device adverse experiences” (28). The current surveillance system relies not only on the FDA and manufacturers but also on hospitals, long-term and ambulatory medical care facilities, health care providers, and patients to report adverse events from medical devices. Postmarket surveillance is designed to identify uncommon but potentially serious device-related adverse events (28). The FDA uses several methods to conduct postmarket surveillance, including spontaneous reporting systems, analysis of large health care databases, scientific studies, registries, and field inspection of facilities.

Spontaneous Reporting Systems

The FDA depends primarily on a passive adverse event reporting system. It relies on patients and the health care industry to identify and report adverse events, including

rare serious occurrences. Manufacturers are required to report to the FDA any medical device–related event or malfunction that may have caused or could cause a serious injury or death (3, 7). Hospitals, nursing homes, and other medical facilities (long-term care facilities, ambulatory surgical facilities, outpatient treatment facilities, and outpatient diagnostic facilities) are required to report serious device-related injuries to the manufacturer and device-related deaths to both the manufacturer and the FDA (1, 3, 7, 31).

The FDA annually receives 80 000 to 120 000 device-related adverse event reports. Most of these reports come from manufacturers (2, 25, 27); only about 5000 come directly from medical facilities (3, 27). Devices with well-known and well-documented adverse event profiles may be subject to less stringent summary reporting, which enables the FDA to more easily review a large number of devices and reports (27).

Health care professionals and patients are also encouraged to report suspected device-related adverse events through the FDA MedWatch program. Suspected events may be reported by telephone, fax, or mail or over the Internet (www.fda.gov/medwatch) (2, 27). The FDA receives approximately 5000 reports through MedWatch each year, and each event is evaluated (2). Nurses are the most frequent reporters (25% of reports), and physicians rarely report events (8% of reports) (2).

On receipt of a report from a manufacturer, health care facility, or health care provider, the FDA evaluates the event to assess its seriousness, the population at risk, and the likelihood of recurrence (2). Reports are entered into a database and triaged for additional evaluation and action (2). Teams of analysts look for patterns that may warrant more investigation (3). In 1995, the Manufacturer and User Device Experience (MAUDE) database, which currently contains more than 300 000 reports, was established to assist with device adverse event reporting and information dissemination (3).

Spontaneous reporting systems have several important limitations. Although manufacturers must report events of which they become aware, they are not required to actively seek out device malfunctions (28). As a result, device-related adverse events are substantially underreported (27). Recently, the FDA specially trained 75 medical facilities (primarily hospitals and nursing homes) in device reporting. These medical facilities make up the newly established Medical Products Surveillance Network, which identifies previously unrecognized problems in both device function and user error in the clinical setting (32, 33).

Other Methods of Postmarket Surveillance

Because of the shortcomings of the spontaneous reporting systems, the FDA uses other methods of postmarket surveillance. On the basis of data from the spontaneous reporting systems, the FDA may conduct or commission a study to further investigate an issue in detail. This addi-

tional surveillance may take the form of a clinical trial, a literature review, an analysis of complaint information, or some other investigation (28). Some products with unknown but potentially serious risks are followed by FDA-mandated registries (27). In general, the FDA has the authority to require that manufacturers implement additional postmarket surveillance on any device when it deems such surveillance appropriate (3, 28, 34).

In addition, the FDA sends trained investigators to manufacturing sites to perform field inspections both on a routine basis and for specific evaluations when irregularities arise (15). Inspections are prioritized to investigate manufacturing facilities with previous violations and facilities manufacturing newly approved life-sustaining devices for which a facility inspection has not been recently conducted (15).

When the FDA identifies a problem or potential problem with a medical device, it may conduct a more in-depth investigation, often with the assistance of the manufacturer, to help determine the root cause of the problem. Problems may be due to manufacturing defects, poor product design, misleading labeling, confusing instructions, patient sensitivity, or other causes.

Depending on the nature and scope of the problem, the FDA may choose to issue a public health advisory or a safety alert (2, 3). A public health advisory is issued when a device with the potential for risk is identified. A safety alert, on the other hand, is issued when a device has actually caused serious injury or death (2, 3). The FDA may also use several enforcement methods to obtain manufacturer compliance. Warning letters may be issued for regulatory violations (24, 27). When violations are recurrent or pose a serious health threat, medical product may be seized (when products are not in compliance with regulations) or injunctions (when manufacturers or personnel are not in compliance with regulations) may be issued (24, 27). Mandatory recalls and premarket approval suspension or withdrawal may be invoked when a reasonable probability of serious harm exists (24, 27). In rare cases, criminal prosecution may be considered (24, 27). Violations of the Federal Food, Drug, and Cosmetic Act may be misdemeanors or felonies (24). Felonies are generally more severe crimes that are obviously criminal and reflect specific intent to defraud (24). Penalties may also include individual fines up to \$250 000 and corporate fines up to \$500 000 for each offense (24).

UNAPPROVED USES OF MEDICAL DEVICES

Physicians and other health care providers have certain responsibilities to ensure the safe use of approved medical devices. Familiarity with the indications and the proper methods for use of the device is of paramount importance. This includes a working knowledge of the device's written instructions and labeling. Adequate, routine device maintenance should also be ensured. In some cases, physicians may wish to use an unapproved medical device or an ap-

proved medical device for an unapproved indication. Physicians should be aware of the FDA regulations that guide the use of medical devices in these circumstances.

Investigational Use

Experimental or investigational use of unapproved devices is strictly regulated by the FDA and requires elaborate informed consent procedures (35). In most cases, an FDA Investigational Device Exemption and institutional review board approval are necessary. Investigational use of an unapproved medical device without appropriate authorization could expose the physician to significant liability.

Emergency Use

Occasions may arise in which a physician believes emergency use of an unapproved medical device is warranted. For a situation to be considered an emergency, several criteria must be met: 1) The patient must have a life-threatening condition that needs immediate treatment, 2) no acceptable alternative for treating the patient is available, and 3) there is no time to use existing procedures to obtain FDA approval because of immediate patient need (15). A physician who uses an unapproved medical device under emergency circumstances is expected to first fulfill several obligations. He or she must 1) obtain independent assessment by an uninvolved physician, 2) obtain informed consent from the patient or legal representative, 3) receive institutional clearance to use the product on an emergency basis, 4) obtain authorization from the institutional review board chairperson, and 5) obtain authorization from the medical device sponsor (for example, the manufacturer or Investigational Device Exemption sponsor) (15). If an Investigational Device Exemption does not exist, the FDA should be notified in writing of the circumstances and outcome of the device's emergency use (15).

Humanitarian Use

Certain medical devices are useful for treating rare diseases. To aid in bringing these products to market despite limited profitability for the manufacturer, these "humanitarian use devices" are exempted from certain requirements (15, 36). Of note, they are exempted from the demonstration of effectiveness. The manufacturer need only demonstrate that the device has "probable" health benefits that outweigh its risks (15). Examples of devices that have been approved under the Humanitarian Use Exemption include a central nervous system stimulator for the treatment of chronic, intractable primary dystonia and a surgical adhesive used as an adjunct in the surgical management of acute thoracic aortic dissections (37, 38). Humanitarian use is acceptable with institutional review board approval or with post hoc approval for life-threatening emergencies (36).

Unapproved or "Off-Label" Uses of an Approved Medical Device

No specific statute or law prevents a physician from using a legally marketed, FDA-approved medical device to treat any disease or condition. This includes using devices

for unapproved off-label indications. In general, the consensus of courts in the United States is that the off-label use of FDA-approved medical devices is part of the practice of medicine and reflects the execution of medical judgment (35). Informed consent standards and court findings vary by jurisdiction, and some courts may require that the FDA regulatory status of a medical device be disclosed to a patient before its use (35). Patients who receive a device in the context of a clinical trial, including those who receive a device in a trial designed to add an FDA-approved indication to an already approved device, must be informed of the investigational nature of the device (35). In all cases, the physician remains obligated to inform the patient of the risks, benefits, and alternatives to using the device (35).

As a general rule, the FDA does not object to off-label use of devices by individual physicians treating specific patients. The FDA does, however, have the authority to take action if the device is likely to be used for a potentially harmful off-label use (26). Furthermore, the physician may not promote the unapproved use of the device and may not formally study the device for an off-label use without FDA Investigational Device Exemption approval (24). This does not prevent physicians from publishing reports of their off-label use of devices, but it is the authors' responsibility to ensure that the reader understands the approval status of the product. Manufacturers may not use these publications to promote the off-label use of the device (15, 24, 39). When devices are used in a manner not specified on the product labeling, manufacturers may be relieved of product liability (2).

Third-Party Payer and Reimbursement Issues

Approval by the FDA, while often necessary, is by itself rarely sufficient to obtain coverage from Medicare, managed care, and third-party payers (3, 40). The Centers for Medicare & Medicaid Services (CMS) (formerly the Health Care Financing Administration) and private insurers may choose not to reimburse an FDA-approved device or an FDA-approved indication for a device. Although the FDA and CMS review scientific data, the legislation and statutes that guide their decision making are different (41). The FDA must determine that a device is "safe and effective" as a condition of approval, whereas CMS must determine that the device is "reasonable and necessary" for the Medicare population as a condition of coverage (41). Historically, "reasonable and necessary" has been ill defined, and CMS has made decisions on a case-by-case basis (41, 42). Although the FDA does not consider issues of cost-effectiveness and CMS does not formally consider issues of cost-effectiveness, cost may play some role in the CMS decision process, particularly for expensive therapies (42–44). Because of differences in the statutes and the review process, FDA and CMS decisions may occasionally diverge.

In July 2002, for example, the FDA approved "prophylactic treatment of patients with a prior myocardial infarction (MI) and ejection fraction (EF) of < 30%" as a

new indication for a manufacturer's implantable cardioverter defibrillator on the basis of the results of a randomized trial (45, 46). However, CMS determined that the evidence was "not adequate" to conclude that implantable cardioverter defibrillators were "reasonable and necessary" for all patients who met the FDA indication. Instead, CMS limited coverage to only higher-risk patients with a QRS duration greater than 120 milliseconds, although this was not an entry criterion for the clinical trial (45). Some but not all third-party payers have chosen to reimburse prophylactic implantation of implantable cardioverter defibrillators on the basis of the broader FDA indication rather than the CMS decision (47).

When FDA indications and insurance coverage conflict, physicians and patients are placed in an awkward position. Although a physician could be liable for not recommending an implantable cardioverter defibrillator to a high-risk patient who meets FDA-approved indications, a patient who accepts such a recommendation may receive a medical bill exceeding \$20 000. In an environment of spiraling health care costs and advancing technology, FDA and CMS decisions will probably continue to occasionally diverge.

CONGRESSIONAL OVERSIGHT OF THE FDA

When concern arose among the public, manufacturers, and Congress about prolonged delays accompanying the FDA device approval process (7, 12, 23, 48), Congress enacted the FDA Modernization Act of 1997 (12, 49). This Act expedited review times by setting time limits on the FDA at various steps in the approval process; by requiring expedited review of devices representing breakthrough technologies or devices for which no alternative exists; by allowing a manufacturer to request in writing, before application for device approval, the specific data that will be required for approval; and by allowing the FDA to use third-party reviewers to evaluate lower-risk devices (12, 13).

Congressional oversight of the FDA occurs by enactment of legislation, by control of the FDA budget, and by confirmation of the FDA commissioner. Each of these processes often but not always occurs in partisan fashion (50). The ease or difficulty of the FDA device approval process affects the speed and cost at which new devices can be brought to market and, therefore, has broader economic implications for manufacturers and the U.S. economy.

The challenge to the FDA has been and remains striking a balance between "rushing a product to market" to allow patients to benefit from medical advances and simultaneously ensuring patient safety. Congressionally legislated time limits for review and approval decisions on new devices, therefore, can "tip the balance" toward speed or safety (51).

The current medical device regulatory system in the United States is the most complex and stringent in the world. Nevertheless, several areas could be targeted to im-

prove overall device safety. Higher physician reporting rates of observed device-related adverse events are critical to the timely detection of device malfunctions. However, as physicians are asked to carry heavier and heavier patient loads, reporting rates are likely to decrease rather than increase. Better use of specially trained sentinel health care facilities that report adverse events in the FDA-initiated Medical Products Surveillance Network may compensate for some of this decrease. Although safety data are currently accessible to health care providers and consumers on the FDA Web site, the process of reviewing the data is tedious and of limited clinical use. Improved search functions and better access to more detailed malfunction data are required. Because much of the malfunction data are confidential and considered proprietary, independent studies of the actual causes and mechanisms of device-related malfunctions are limited. Improved understanding of the underlying causes of device failure could lead to improved device design, improved manufacturing, and safer use.

CONCLUSION

Medical devices contribute to the health and well-being of millions of patients, but they do not always function as anticipated. The safety and effectiveness of medical devices in the United States are under the purview of the FDA. The FDA's task is primarily risk assessment, which is performed through the processes of premarket and post-market evaluation. The desire to rush a new product or technology to market must be balanced carefully against the desire to ensure the safety of those who will benefit from the device. The FDA, Congress, manufacturers, the public, and physicians each play a vital role in the safe and effective use of medical devices.

From Brigham and Women's Hospital, Boston, Massachusetts.

Disclaimer: The opinions expressed in this paper are those of the author and do not necessarily reflect the opinion of the U.S. Food and Drug Administration.

Potential Financial Conflicts of Interest: *Consultancies:* U.S. Food and Drug Administration Center for Devices and Radiologic Health and Circulatory Systems Device Panel of the Medical Devices Advisory Committee.

Requests for Single Reprints: William H. Maisel, MD, MPH, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115; e-mail, wmaisel@partners.org.

References

1. Monsein LH. Primer on medical device regulation. Part I. History and background. *Radiology*. 1997;205:1-9. [PMID: 9314952]
2. Improving patient care by reporting problems with medical devices. *Med Watch*. Rockville, MD: Department of Health and Human Services, U.S. Food and Drug Administration, HF-2; September 1997.
3. Kessler L, Richter K. Technology assessment of medical devices at the Center for Devices and Radiological Health. *Am J Manag Care*. 1998;4 Spec No:SP129-

35. [PMID: 10185989]
4. Pritchard WF Jr, Carey RF. U.S. Food and Drug Administration and regulation of medical devices in radiology. *Radiology*. 1997;205:27-36. [PMID: 9314955]
5. Center for Devices and Radiologic Health. Accessed at www.fda.gov/cdrh/index.html. on 20 December 2003.
6. Food, Drug, and Cosmetic Act. 21 USC § 201(h).
7. Munsey RR. Trends and events in FDA regulation of medical devices over the last fifty years. *Food Drug Law J*. 1995;50 Spec:163-77. [PMID: 10343041]
8. Moss AJ, Hamburger S, Moore RM, Jeng LL, Howie LJ. Use of selected medical device implants in the United States, 1988. *Advance Data from Vital and Health Statistics of the National Center for Health Statistics*; 191:1-24. Hyattsville, MD: National Center for Health Statistics; 26 February 1991.
9. Weinstein JW, Mazon D, Pantelick E, Reagan-Cirincione P, Dembry LM, Hierholzer WJ Jr. A decade of prevalence surveys in a tertiary-care center: trends in nosocomial infection rates, device utilization, and patient acuity. *Infect Control Hosp Epidemiol*. 1999;20:543-8. [PMID: 10466554]
10. Birnbaum D. Systems are changing; where can they be improved? *Clin Perform Qual Health Care*. 1999;7:97-9. [PMID: 10747575]
11. Pearson M. Twenty-first century health care. *Med Device Technol*. 1999;10:14-7. [PMID: 10387620]
12. Pilot LR, Waldmann DR. Food and Drug Administration Modernization Act of 1997: medical device provisions. *Food Drug Law J*. 1998;53:267-95. [PMID: 10346685]
13. Merrill RA. Modernizing the FDA: an incremental revolution. *Health Aff (Millwood)*. 1999;18:96-111. [PMID: 10091437]
14. Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act. Pub L No. 94-295, 90 Stat 539 (1976).
15. Monsein LH. Primer on medical device regulation. Part II. Regulation of medical devices by the U.S. Food and Drug Administration. *Radiology*. 1997;205:10-8. [PMID: 9314953]
16. Medical devices; exemption from premarket notification requirements; class I devices; technical amendment. Final rule; technical amendment. *Fed Regist*. 2001;66:38786-819. [PMID: 11725800]
17. Smith JJ, Shyjan AM. Defining "least burdensome means" under the Food and Drug Administration Modernization Act of 1997. *Food Drug Law J*. 2000;55:435-47. [PMID: 11824468]
18. Medical devices; exemption from premarket notification and reserved devices; class I. Food and Drug Administration, HHS. Final rule. *Fed Regist*. 2000;65:2296-323. [PMID: 11010655]
19. Donawa ME. Use and recognition of consensus standards in US premarket submissions. *Med Device Technol*. 1999;10:13-7. [PMID: 10387610]
20. 510(k) Summary of Safety and Effectiveness. K031141. Asap endoscopic products. June 2003. Accessed at www.fda.gov/cdrh/pdf3/k031141.pdf on 7 August 2003.
21. Summary of Safety and Effectiveness. PMA 010012. CONTAK CD CRT-D System. June 2002. Accessed at www.fda.gov/cdrh/pdf/P010012b.pdf on 7 August 2003.
22. Summary of Safety and Effectiveness Data. PMA 990026. GlucoWatch Automatic Glucose Biographer. 22 March 2001. Accessed at www.fda.gov/cdrh/pdf/P990026b.pdf on 7 August 2003.
23. Sapirstein W, Alpert S, Callahan TJ. The role of clinical trials in the Food and Drug Administration approval process for cardiovascular devices [Editorial]. *Circulation*. 1994;89:1900-2. [PMID: 8149556]
24. Monsein LH. Primer on medical device regulation. Part III. Regulatory mechanisms and import/export regulation. *Radiology*. 1997;205:19-25. [PMID: 9314954]
25. Feigal DW, Gardner SN, McClellan M. Ensuring safe and effective medical devices. *N Engl J Med*. 2003;348:191-2. [PMID: 12529457]
26. Nelson DB, Block KP, Bosco JJ, Burdick JS, Curtis WD, Faigel DO, et al. Medical device evaluation by the Food and Drug Administration (FDA). *Gastrointest Endosc*. 2001;53:880-4. [PMID: 11375624]
27. Managing Risks from Medical Product Use: Creating a Risk Management Framework. Report to the FDA Commissioner from the Task Force on Risk Management. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration; May 1999.
28. Postmarket surveillance. Final rule. *Fed Regist*. 2002;67:38878-92. [PMID: 12053947]
29. O'Neill WW, Chandler JG, Gordon RE, Bakalyar DM, Abolfathi AH, Castellani MD, et al. Radiographic detection of strut separations in Bjork-Shiley convexo-concave mitral valves. *N Engl J Med*. 1995;414-9. [PMID: 7616990]
30. Safe Medical Devices Act of 1990. Pub L No. 101-629, 104 Stat 4511 (1990).
31. Medical device and user facility and manufacturer reporting, certification and registration; delegations of authority; medical device reporting procedures; final rules. *Fed Regist*. 1995;60:63577-606.
32. Center for Devices and Radiologic Health Annual Report Fiscal Year 2000. January 2001. Accessed at www.fda.gov/cdrh/annual/fy2000/annualreport-2000-5.html on 16 July 2003.
33. Hospital and nursing homes participating in MedSun. *Medical Product Surveillance Network News*. 2003;3:21-2.
34. Medical devices; device tracking. Final rule. *Fed Regist*. 2002;67:5943-52. [PMID: 11838471]
35. Smith JJ, Berlin L. Informed consent when using medical devices for indications not approved by the Food and Drug Administration. *AJR Am J Roentgenol*. 1999;173:879-82. [PMID: 10511140]
36. Medical devices; humanitarian use of devices—FDA. Final rule. *Fed Regist*. 1998;63:59217-22. [PMID: 10187383]
37. Humanitarian Use Devices: Listing of CDRH Humanitarian Device Exemption Summaries of Safety and Possible Benefit. H020007. Medtronic Activa Dys-tonia Therapy. April 2003. Accessed at www.fda.gov/cdrh/ode/hdeinfo.html#2 on 4 November 2003.
38. Humanitarian Use Devices: Listing of CDRH Humanitarian Device Exemption Summaries of Safety and Possible Benefit. H990007. BioGlue Surgical Adhesive. December 1999. Accessed at www.fda.gov/cdrh/ode/hdeinfo.html#2 on 4 November 2003.
39. Basile EM, Armentrout E, Reeves KN. Medical device labeling and advertising: an overview. *Food Drug Law J*. 1999;54:519-33. [PMID: 11824451]
40. Are you really ready for FDA approval? Coverage and reimbursement for medical devices. *Health Law*. 2001;6:1-3. Accessed at www.hklaw.com/publications/newsletters.asp?ID=189&Article=992 on 20 December 2003.
41. Medicare program; revised process for making Medicare national coverage determinations. *Fed Regist*. 2003;68:55634-41.
42. Cusack B. Medicare won't fully cover Cheney-type pacemakers. *The Hill*. 4 June 2003. Accessed at www.hillnews.com/news/060403/pacemaker.aspx on 4 November 2003.
43. Medicare proposal will help standardize coverage decisions for additional treatments. *Medicare News*. 11 May 2000. Accessed at <http://cms.hhs.gov/media/press/release.asp?Counter=202> on 4 November 2003.
44. American College of Cardiology. CMS, FDA taking closer look at cost effectiveness of drugs, devices. *Advocacy Weekly*. 16 December 2002. Accessed at acc.org/advocacy/weekly/archives/dec_02/121602.htm#fda on 20 December 2003.
45. Phurrough S, Farrell J, Chin J. National Coverage Determination (NDC) on Implantable Defibrillators (#CAG-00157N). 6 June 2003. Accessed at <http://cms.gov/coverage/download/id39-5.pdf> on 20 December 2003.
46. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-83. [PMID: 11907286]
47. Some HMOs to cover cost of heart device. *Los Angeles Times*. 14 June 2003.
48. Kimbell JJ. The U.S. medical device industry: entrepreneurs' future hinges on reforms at the Food and Drug Administration. *Food Drug Law J*. 1996;51:339-43. [PMID: 11822328]
49. Food and Drug Administration Modernization Act of 1997. Pub L No. 105-115, 111 Stat 2295 (1997).
50. Dickinson JG. Another bloody season in the FDA—Congress wars? MDDI. January 1997. Accessed at devicelink.com/mddi/archive/97/01/018.html on 20 December 2003.
51. Dickenson JG. Congress enacts device law and confirms FDA chief. MDDI. November 2002. Accessed at devicelink.com/mddi/archive/02/11/004.html on 20 December 2003.