

## Technology Assessment of Medical Devices at the Center for Devices and Radiological Health

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### **Abstract**

**We reviewed the Food and Drug Administration's regulatory process for medical devices and described the issues that arise in assessing device safety and effectiveness during the postmarket period. The Center for Devices and Radiological Health (CDRH), an organization within the Food and Drug Administration, has the legal authority and responsibility for ensuring that medical devices marketed in the United States are both reasonably safe and effective for their intended use. This is an enormous challenge given the diversity of medical devices and the large number of different types of devices on the market. Many scientific and regulatory activities are necessary to ensure device safety and effectiveness, including technology assessment, albeit in a manner quite different from that of conventional technology assessment. The basic approach taken at the CDRH to ensure device safety and effectiveness is to develop an understanding of the way in which a medical device works and how it will perform in clinical situations.**

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**T**he Center for Devices and Radiological Health (CDRH), an organization within the Food and Drug Administration (FDA), has the legal authority and responsibility for ensuring the safety and effectiveness of all medical devices and the safety of radiation-emitting products marketed in the United States. Congress charged the FDA with this responsibility beginning with the 1976 Medical Device

Amendments<sup>1</sup> to the Food, Drug, and Cosmetic Act<sup>2</sup> and the subsequent Safe Medical Devices Amendments of 1990<sup>3</sup> and the FDA Modernization Act of 1997,<sup>4</sup> which was signed by President Clinton on November 21, 1997.

Among the most important functions of the CDRH are clearance for marketing new products and monitoring or assessing the performance of products already on the market. The procedures used by the FDA to review medical devices have undergone considerable transformation over the past decade and are undergoing transformation once again. Both the 1976 and 1990 laws provided the FDA with a substantial degree of flexibility in determining the requirements for clearing or approving a medical device and monitoring its safety and effectiveness once on the market.

The CDRH's responsibility for ensuring device safety and effectiveness is daunting, given the diversity of medical devices on the market. Simple devices, such as latex examination gloves and blood glucose test strips, are regulated, as are hospital beds and wheelchairs, pacemakers and implantable cardioverter defibrillators, and large capital equipment such as mammography machines and magnetic resonance imaging equipment. At present, more than 500,000 different medical device models and products are marketed in the United States. Assessing all these devices is clearly a challenge. Consider, for example, that assessment of in vitro diagnostics is considerably different from that for digital mammography.

The language Congress adopted in authorizing the CDRH recognizes that devices are different from drugs. The FDA has to obtain reasonable assurance of safety and effectiveness of a medical device in contrast to the higher standards set for drug approval, which typically require that safety and efficacy be demonstrated in at least two randomized, double-blind, placebo-controlled trials. The FDA generally does not compare more than one technology for a specific clinical condition, which is often required in conventional technology assessments.

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## GETTING TO MARKET

A medical device can enter the market in two different ways. Most often, a device can enter the market if it can be shown to be substantially equivalent to a legally marketed product being sold at the time of the 1976 Amendments (which grandfathered in most products on the market at the time) or can be shown to be substantially equivalent to a product since legally marketed. The product to which the new product is shown equivalent is called a "predicate device," and the path to market requires that the manufacturer of the new device file a premarket notification called a 510(k). By statute, the FDA must notify the firm within 90 days as to whether it considers the new product of substantial equivalence to the predicate device. The CDRH received 5,297 510(k) applications in fiscal year 1996 (October 1, 1995 to September 30, 1996) and 5,049 in fiscal year 1997; it cleared more than 5,563 and 5,155 510(k)s during FY1996 and FY1997, respectively (including some from previous years). If the FDA has concerns about the safety or effectiveness of a product, it may need to reclassify the product and then the device may need to undergo a premarket approval (PMA) process, which may be required not only of new devices but also for modifications to current devices and changes in labeling for these devices.

New devices without predicates can enter the market through the PMA process. In contrast to the considerable number of 510(k) applications submitted, the CDRH received only 44 original PMA submissions in FY1996 and 70 in FY1997. These devices

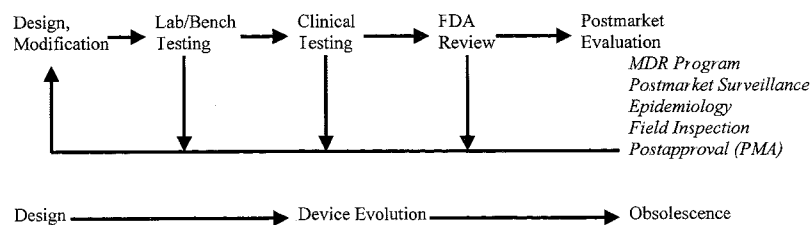
usually include high-risk products or those devices so new that little is known about them. The PMA process for medical devices includes more than just the clinical aspects of safety and performance. It also includes design information, design controls, and detailed manufacturing process information. In addition, the manufacturer must submit the results of nonclinical laboratory testing, which may cover microbiologic, toxicologic, immunologic, biocompatibility, stress, wear, shelf life or expiry, and analytic aspects of the device.

### Approval Process for Medical Devices

The pathway to market for a medical device is illustrated in Figure 1. When a device is invented or modified, the manufacturer or sponsor works with the CDRH to determine whether the device is a new product or a modification of one already legally marketed. After the invention or modification phase, devices typically are tested in the laboratory for performance characteristics. Devices used for diagnostic purposes may require different review procedures and different clinical data than those for therapeutic use. For example, diagnostic devices almost always must be tested in the intended patient population, since bench testing is rarely sufficient to gauge safety and effectiveness. In some cases, device features may be tested against international standards to determine whether they conform to those standards.<sup>4</sup> This approach speeds the approval process, since the CDRH is assured that the device meets certain standards and CDRH staff members need not review the details of device testing.

In evaluating a device's market readiness, CDRH reviewers must weigh the product's benefits against its known or potential risks. The manufacturer must provide credible scientific data on both benefits and risks. Firms that do not disclose evidence of a device's risks before or after it is marketed are subject to various legal regulatory actions. Although considerations of cost-effectiveness do not fall under the FDA's purview, third-party payers consider many of the risk and benefit factors identified by the CDRH in as-

**Figure 1.** Pathway to Market for a Medical Device



FDA = Food and Drug Administration; MDR = medical device reporting; PMA = premarket approval.

sessing devices for reimbursement. Payers may take into account the costs of immediate and long-term treatment, likelihood of success with various therapies, and expected cost of retreatment or delayed treatment. Payers may also evaluate devices by category, based on published literature or large studies assessing general clinical outcomes by treatment method, as opposed to the device-specific reviews conducted by the CDRH.

For many medical devices, but certainly not all, clinical trials are required for clearance to market. This particular issue is at the core of a considerable controversy in the medical device community. Before 1990, few medical devices were evaluated in clinical trials to determine their safety and effectiveness. However, serious problems with certain products, such as the Bjork-Shiley heart valve, prompted the FDA to systematically review its device approval process. In 1991, a review group convened by the FDA commissioner and cochaired by Robert Temple, MD, and Ann Witt, JD, of the FDA's Center for Drug Evaluation and Research concluded that medical devices needed to undergo more rigorous evaluation. Although the CDRH has begun to request more clinical trials, the FDA also recognizes that an approval process created for drugs may not necessarily be suited to all medical devices. Thus the CDRH is implementing a system for device approval that balances the need for clinical data with understanding of device performance obtained from engineering and bench test data reviews.

When a manufacturer considers a device ready for clinical study, the firm applies to the FDA for an Investigational Device Exemption (IDE), requesting permission to use the device on patients in an experimental situation. For significant risk devices, the manufacturer presents the design and rationale for the study to the Institutional Review Board of the CDRH for evaluation and approval. New devices are not to be used on patients without an IDE, with the exception of emergency or compassionate use. With passage of the FDA Modernization Act of 1997, the device manufacturer and the CDRH can now negotiate an agreement that successful completion of clinical studies recommended by the CDRH (ie, if results confirm safety and effectiveness) will lead to device approval.

#### Approval Process Examples

To better understand how the CDRH assesses the clinical performance of medical devices, we will examine the approval process for the following four devices: an implantable cardioverter defibrillator evaluated in a randomized clinical trial; intraocular

lenses evaluated through performance grids; Thin-Prep™ (Cytoc Corp., Marlborough, MA) for Pap smears, also evaluated in a clinical trial; and digital mammography evaluated through substantial equivalence (ie, a 510(k) application).

To obtain approval for an implantable cardioverter defibrillator, the manufacturer submitted data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT),<sup>5</sup> a large, international, multicenter, randomized, controlled clinical trial. Results from MADIT showed that the device was superior to conventional drug therapy for a specific cardiovascular

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indication (asymptomatic nonsustained ventricular tachycardia in high-risk patients with heart disease), with a death rate one half that of drug therapy.<sup>5</sup> Although implantable cardioverter defibrillators were introduced in 1980<sup>6</sup> and used extensively in patients with symptomatic sustained ventricular tachycardia, MADIT was the first randomized trial demonstrating a significant reduction in mortality in asymptomatic patients. The most remarkable aspect of the approval process for this product is that the sponsor submitted data early to the CDRH and came to the Center for an interactive review that lasted 6 days, at which time the product was approved. This inordinately rapid market approval (the average review time exceeds 180 days) was enabled by the outstanding randomized controlled trial, which made evident both the benefits and risks of the device compared with conventional therapy. The CDRH can easily assess the risk-benefit profile of a device when it has clinical trial data and especially when the product has been previously approved and the manufacturer is seeking only a new,

although significant, indication. The combination of the clinical trial data and the rapid interactive review and approval was groundbreaking for CDRH and could serve as a model for future efforts.

The pathway to approval for intraocular lenses was much different from that for the implantable cardioverter defibrillator. Both the CDRH and the ophthalmologic community have extensively studied the performance of intraocular lenses.<sup>7</sup> Thus new randomized trials are not the only means available to fairly evaluate these products. As an alternative to the clinical trial, the CDRH used the extensive literature in the field to develop and publish a performance grid, which provides a documented reference or set of historical controls against which to measure patient response to a new technology. Because the ophthalmologic community is familiar with this approach, new intraocular lenses are evaluated in single-arm studies with their results compared to the grid for evidence of effectiveness. Use of the performance grid has proved to be an efficient strategy in an area where essential safety issues are not an issue for new device application.

Data collected by the manufacturer of ThinPrep, a system that helps clinicians prepare Pap smear slides, were substantial. Pap smears prepared using ThinPrep or conventional methods from more than 7,000 consecutive women entering a study clinic were examined and compared by a reference pathologist. The initial study protocol was a blinded, split-sample, matched-pair trial. In addition to comparisons of readings from ThinPrep and conventionally prepared slides, a reference pathologist reviewed all discrepant and positive slides from all clinical sites in a blinded fashion to provide an objective review of the results. Because no confirmatory readings were done for negative/negative combinations, specificity could not be measured. The original application for this product did not contain sufficient clinical data, and the firm complied with the CDRH's request for more information. Assessing the "risk" associated with a product of this type is difficult because the relative infrequency of disease makes finding pathologically confirmed cancers unlikely even when a significant number of women are tested. However, extensive clinical studies showed that the ThinPrep method helped identify lesions thought to be precursors of cancer or clinically meaningful.<sup>8</sup> The National Institutes of Health is currently conducting additional studies using the ThinPrep method, and more informative data may become available.

For almost 20 years, film-screen mammography has been the technology of choice for screening

women for signs of breast cancer. This method involves placing a woman's breast on top of a radiographically sensitive plate, which is developed after x-rays are passed through the breast. Irradiating the breast has known risks, and one of the major developments in breast cancer screening over the past decade has been the systematic reduction in radiation exposure and an improvement in images. In the past 5 years, we have seen the development of digital mammography, which is similar to current film-screen or analog mammography. Again, x-rays are used but instead of a photographic plate, the image receptor consists of a media that captures breast images digitally. Digital mammography has two distinct advantages: transportability of information and the ability to change a variety of image features, such as contrast, without retaking images or redeveloping film. Because digital mammography works in a similar fashion as the technology it is intended to replace, CDRH is considering whether it should be approved through the 510(k), or substantial equivalence, process.

However, the CDRH cannot readily assess the risks and benefits of digital mammography unless sufficient data are collected to demonstrate whether it is equivalent to or better than current methods for detecting cancer. It is expected that more than 10,000 women would need to undergo both analog and digital mammography to obtain sufficient data.<sup>9</sup> Yet the similarity of the new technology to older methods encouraged the FDA to develop and publish guidelines for digital mammography, suggesting that an agreement study between the two methods with a sample size of approximately 500 women with half abnormal analog mammograms would yield sufficient information on the similarity or substantial equivalence of the two methods to allow market entry. If a manufacturer pursues this option, the CDRH probably will require systematic data collection in the postmarket period to further evaluate the clinical characteristics of the technology in a larger population.

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#### POSTMARKET ASSESSMENT

Most medical devices marketed today were either on the market before the 1976 Amendments or are considered substantially equivalent to such products or their successors. The FDA has four means of ensuring the continued safety and effectiveness of cleared medical devices: the medical device reporting program, postmarket surveillance studies program,

epidemiologic investigations, and field inspections of facilities.

The medical device reporting program began in 1984 with the institution of mandatory reporting from manufacturers of medical devices to the FDA. Manufacturers must report any incident in which their medical device may have caused or contributed to a death or serious injury or illness or any device malfunction that could cause death or serious injury. Passage of the Safe Medical Devices Act of 1990<sup>3</sup> required user facilities, including hospitals, nursing homes, and outpatient diagnostic or therapeutic facilities, to report to manufacturers and the FDA any serious injury, illness, or death caused or contributed to by a medical device. Mandatory reporting regulations for user facilities went into effect on July 31, 1996. In addition to the mandatory program, healthcare professionals are encouraged to voluntarily report any adverse events associated with a medical device. Ninety-five percent of the more than 80,000 reports the FDA processed during calendar year 1996 were from manufacturers, and the remaining reports were equally divided between those from user facilities and those from healthcare professionals.

How does the FDA use the medical device reporting program for technology assessments? Each of the reports are entered into the FDA's database, which now contains more than half a million records on problems with medical devices. The reports are reviewed by a team of analysts (mostly nurses) who look for patterns or unusual occurrences that deserve further investigation. Follow-up investigations sometimes include inspections of the manufacturing facility or queries directed to the manufacturer to answer concerns about the safety or effectiveness of a medical device. If a significant problem is found, the FDA may issue a Safety Alert or Public Health Advisory to notify the healthcare community of the problem.

Compared with mandatory and voluntary reporting of device problems, the postmarket surveillance studies program is a more systematic attempt at assessing safety and effectiveness once a device is on the market. Under Section 522 of the statutory authority given to the FDA in 1990,<sup>3</sup> the FDA could require manufacturers to conduct postmarket surveillance studies under the agency's guidance. Under the required postmarket surveillance studies program, the FDA could require studies on the safety and effectiveness of certain devices, usually high-risk or implantable devices that have life-supporting or life-sustaining uses, such as pacemakers and heart valves. Twenty-six devices fell under the required postmar-

ket surveillance studies program. Under the discretionary postmarket surveillance studies program, the FDA can request postmarket surveillance studies at its discretion, as it did for polyurethane foam-covered breast implants, for example. These discretionary studies can range from short-term trials to investigations lasting up to 10 years, depending on the nature of the question being examined. The FDA Modernization Act of 1997<sup>3</sup> changed the 1990 law by revoking the required postmarket surveillance studies program but leaving substantially intact the FDA's discretionary postmarket surveillance authority. A drawback to the postmarket surveillance study program is that these studies usually focus on only one or two aspects of the safety or effectiveness of a device and do not provide an overall examination of the risks and benefits associated with the device.

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The FDA also assesses device safety and effectiveness through postmarket epidemiologic investigations. Primarily using secondary data already available, investigators in the FDA's epidemiology branch conduct a variety of studies on the use of and problems with medical devices on the market. A typical database used by the epidemiology branch is that of the Health Care Financing Administration (HCFA) and its Medicare program. Through epidemiologic analysis of the Medicare database, investigators found specific patterns of home oxygen use for different types of oxygen equipment. Ongoing epidemiologic investigations include studies of coronary stents and use of mammography. Once again, although these are systematic investigations of certain aspects of device technology, epidemiologic

studies do not represent a full technology assessment of the device under study.

The final means with which the FDA can ensure postmarket safety and effectiveness of medical devices is through field inspections of manufacturing facilities. Trained investigators visit manufacturing sites on a routine basis as well as "for cause" to examine product production. The most important part of this inspection is determining whether the manufacturer complies with Good Manufacturing Procedures (GMPs). These procedures provide a systematic method of documenting product production that helps ensure a consistently high-quality product. Recently, the FDA made changes in GMPs to conform with international quality systems regulations.

### Postmarket Assessment Examples

The CDRH's ability to evaluate medical devices once they are marketed is illustrated by the following two examples. In 1995, as part of the medical device reporting program, an analyst spotted an increase in the number of severe reactions to the placement of a family of intravenous catheters, with a particularly sharp increase in the number of reports of reactions to a midline catheter designed to provide moderate-term (up to several weeks) administration of intravenous fluids.<sup>10</sup> These reactions appeared similar to anaphylactic syndromes. At considerable expense, the manufacturer performed extensive allergy testing and concluded that the unique material used in the catheters was an unlikely source of the problem. After the publication of an article from the medical device reporting program, a subsequent article from an academic center,<sup>11</sup> and an accompanying editorial suggesting a product problem,<sup>12</sup> negotiations with the company ensued. Although the FDA did not order a postmarket surveillance study, the firm voluntarily agreed to a concurrently controlled but non-randomized study of approximately 6,000 patients with the firm's catheter and two comparison devices. This study would have been the largest single study performed to evaluate the clinical performance of these catheters. However, the study was stopped almost immediately after it began because the company voluntarily withdrew its catheters from the market.

In September 1996, Connors et al<sup>13</sup> published a landmark article citing significantly higher mortality rates for patients in critical or intensive care units who had a pulmonary artery catheter inserted. Pulmonary artery catheters, also called Swan-Ganz or right heart catheters, have been in use since 1970. This well-done observational epidemiologic study involved thousands of patients who had one of nine different

diseases. Connors et al found that patients with pulmonary artery catheters had up to a 25% higher mortality rate than those without such catheters, even when controlling for morbidity and other putatively related factors. This finding prompted two well-known clinicians to call for either definitive randomized trials with the device or an FDA moratorium on the product.<sup>14</sup>

Pulmonary artery catheters have been a staple of intensive care management for almost 30 years and have considerably improved clinicians' ability to manage patients in difficult critical care situations. A national workshop on the topic led to a number of recommendations, including implementation of both a national education program to improve the understanding and use of pulmonary artery catheters in clinical practice and several randomized, controlled trials on the use of the device. Controlled trials appear both feasible and highly advisable in patients with congestive heart failure and those with acute respiratory distress syndrome. These studies, if completed in a timely fashion, may provide the FDA with the information it now lacks. Once the FDA has appropriate data, it might call for changes in the labeling or instructions for use of the device, mandatory training in use of the device, or restrictions on use of the device to maximize its effectiveness and minimize the indirect harm resulting from pervasive and perhaps inappropriate use.

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### DISCUSSION

The number and variety of medical devices marketed in the United States poses an enormous challenge for CDRH staff members, who must evaluate the risks and benefits of each product—a process at the core of technology assessment. However, ensuring that medical devices are both safe and effective in the absence of clinical trial data is difficult. Since the early 1990s, the FDA has increased the rigor of device evaluation, leading to more randomized clinical trials and a better appreciation of the risks and benefits of new device technology.

For managed care and other third-party payers, the FDA approval and clearance process represents a minimum threshold in their consideration of coverage for medical devices. The link between the FDA clearance and approval process and payment by the HCFA, its contractors, and other carriers is somewhat varied. A recently signed interagency agreement between the FDA and HCFA allows HCFA to move away from its policy of payment for legally marketed

products to payment for legally distributed products. Under this agreement, HCFA can reimburse for most experimental devices that are under clinical investigation with an approved IDE application. Because devices must also meet additional HCFA criteria, HCFA does not automatically pay for all investigational devices.

Within the context of their payment policies, managed care plans could certainly borrow from the FDA-HCFA agreement and pay for distributed devices under investigation for specific indications. Generally, large third-party or managed care organizations perform their own technology assessments. However, payers could benefit by working with CDRH staff members by using the understanding of device technology that FDA staff possess.

Reviewers and product analysts at the CDRH have a variety of regulatory and scientific mechanisms with which they can control market entry for new technology and evaluate existing technology. The clinical community and managed care organizations also play a role in ensuring device safety and effectiveness. For example, the clinical community must pose the critical questions that relate to medical devices. Indeed, the device industry often responds to the needs of patients largely identified by clinicians and caregivers. In addition, representatives of the academic community have prominent roles on FDA advisory committees that review new devices and advise on the approval of PMA applications. Thus they command a position of importance in setting the standards for clinical studies. As clinicians, clinical trial experts, and statisticians have become part of the approval process, scientific rigor has increased.

Large managed care organizations may benefit from developing technology and its assessment in a unique way. A "marriage" between the device industry and managed care makes sense. Many devices make claims not only of effectiveness but also of cost-effectiveness, and one of the best platforms for investigating cost-effectiveness is the managed care environment. Here, with appropriate controls, a managed care organization can make a fair assessment of a new device, although this will require a commitment from the managed care company and a partnership with the medical device industry. Patients would benefit greatly from a systematic evaluation of medi-

cal device technology regardless of the setting. Evaluation in a managed care environment provides but one opportunity to ensure that medical device technology in the United States is both safe and effective.

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