



Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years

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Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process; Institute of Medicine

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MEDICAL DEVICES AND THE PUBLIC'S HEALTH

THE FDA 510(k) CLEARANCE PROCESS AT 35 YEARS

Committee on the Public Health Effectiveness of the
FDA 510(k) Clearance Process

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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Willing is not enough; we must do.”*
—Goethe



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This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Preface

The vast majority of the medical devices used in health care in the United States that are reviewed by the US Food and Drug Administration (FDA) before entering the marketplace are cleared (not approved) for human use in a process called premarket notification, or the 510(k) clearance process, named after Section 510(k) of the authorizing legislation passed by Congress in 1976. Stimulated by reports of problems with several 510(k)-cleared devices, the public, legislators, the Government Accountability Office, the Department of Health and Human Services Office of the Inspector General, and the courts, including the Supreme Court, have all questioned the logic and value of the 510(k) clearance process being used by a federal agency charged with responsibility for protecting and promoting the public's health. After 35 years, at a time of rapidly changing science and technology, questions persist about whether the 510(k) process is protecting and promoting the public's health. Thus, the FDA asked the Institute of Medicine (IOM) to evaluate the 510(k) clearance process and to make recommendations aimed at protecting the health of the public while preserving the legitimate interests of industry and patients by making available a mechanism to achieve timely access of medical devices to the market.

The committee determined that it could not evaluate the 510(k) clearance process for bringing devices to market in isolation; it was necessary to understand the full spectrum of devices reviewed by the FDA—from the simplest tongue depressor to the most complex implantable devices. The 510(k) clearance process, the mechanism used for premarket review of most Class II devices, is embedded in the vast middle. In reviewing the legislative and regulatory history of the 510(k) program, the committee found that it was designed in 1976 to provide only a determination of the substantial equiva-

lence of a new device to an already marketed (predicate) device; it was not designed to determine whether a new device provides a reasonable assurance of safety and effectiveness or whether it promotes innovation. That finding complicated the committee's work in that the FDA, in the charge to the committee, stated that the goals of the 510(k) clearance process are to "make available to consumers devices that are safe and effective" and to "promote innovation in the medical device industry." The committee struggled with how to address the conflict between the legislative framework of the program and the FDA's stated goals.

The report lays out the committee's rationale and approach for addressing this conflict and provides recommendations to the FDA that it believes will result in an improved regulatory system for bringing Class II medical devices to market. The recommendations are focused on strengthening the science base needed to make better-informed regulatory decisions and on giving the FDA the tools that it needs to identify and remove problematic devices from the market. The committee believes that taking the recommended steps will generate the information needed to design a robust regulatory framework for Class II devices. The new framework would increase the public's confidence that safe and effective medical devices are being made available in a timely manner.

Because of the high visibility of concerns about the 510(k) clearance process, the FDA has undertaken its own internal study in parallel with the IOM study to determine how the process might be improved within the FDA's existing legislative authorities. Although IOM was not specifically charged with weighing in on or critiquing the FDA's recommendations, the committee did use the FDA's data and analyses in reaching its own conclusions and recommendations.

I would like to thank the members of the committee for their incredibly hard work over the past 16 months. They came from very different backgrounds and perspectives on the development and use of devices for human health care. The time that the committee members invested in this study was considerable. Although their discussions and deliberations often were spirited, they collaborated effectively and reached consensus on the findings, conclusions, and recommendations.

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David R. Challoner, *Chair*
Committee on the Public Health Effectiveness of the
FDA 510(k) Clearance Process

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Acronyms and Abbreviations

AIMDD	active implantable medical devices
ALJ	administrative law judge
CA	competent authority
CART	Clinical Assessment, Reporting, and Tracking program
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CEN	European Committee for Standardization
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
DEN	Device Experience Network
DELTA	Data Extraction and Longitudinal Time Analysis
DHR	device history record
EHR	electronic health record
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FTC	Federal Trade Commission
FTE	full-time equivalent

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ABBREVIATIONS

FY	fiscal year
GAO	Government Accountability Office (formerly General Accounting Office)
GHTF	Global Harmonization Task Force
GMP	good manufacturing practices
HHS	Department of Health and Human Services (formerly Department of Health, Education, and Welfare)
HIMA	Health Industry Manufacturers Association
IG	inspector general
IOM	Institute of Medicine
IVDD	in vitro diagnostic medical devices
MAUDE	Manufacturer and User Device Experience database
MD EPINET	Medical Device Epidemiology Network
MDA	Medical Device Amendments
MDR	medical-device report
MedSun	Medical Product Surveillance Network
NB	notified body
NCDR ICD	National Cardiovascular Data Registry for implantable cardioverter defibrillators
NDA	new drug application
NSE	not substantially equivalent
OC	Office of Compliance
OCP	Office of Combination Products
ODE	Office of Device Evaluation
OMB	White House Office of Management and Budget
ORA	Office of Regulatory Affairs
OTS	off-the-shelf
PMA	premarket approval
QSR	quality-system regulations
SE	substantially equivalent
SMDA	Safe Medical Devices Act
STED	summary technical document
UDI	unique device identification

Summary

Prior to the Medical Device Amendments (MDA) of 1976, medical devices generally had not undergone premarket review by the US Food and Drug Administration (FDA). The MDA created three classes of device types on the basis of the risks posed and the ability of postmarket controls to manage them (see Box S-1). Each device type includes a number of devices. As originally contemplated, the high-risk category (Class III) would require FDA review and approval, through the premarket approval (PMA) process, before a device could be marketed. The moderate-risk and low-risk categories (Class II and Class I, respectively) would not require as rigorous a review. Rather, device manufacturers would be required to notify the FDA at least 90 days before they marketed such a device. This premarket-notification requirement was contained in Section 510(k) of the Federal Food, Drug, and Cosmetic Act and is commonly referred to as 510(k) notification or 510(k) clearance.

A device not on the market at the time of the enactment of the MDA (a “postamendment” device) would be required to demonstrate through a 510(k) notification that it was “substantially equivalent” to a “preamendment” device and, for Class II devices, complied with the applicable performance standard promulgated by the FDA. If the new device were substantially equivalent, it would be classified in the same class, and cleared for marketing subject to the same terms and conditions, as that preamendment device (for example, conformance to a performance standard). Postamendment devices that were not substantially equivalent to any preamendment device would be automatically placed in Class III and would require either PMA or reclassification by the FDA to Class I or Class II to enter the market.

BOX S-1

The Three Device Classes

- Class I devices are those for which the general regulatory controls should be sufficient to provide reasonable assurance of safety and effectiveness. Class I may also include any device on which there is insufficient information to judge the adequacy of the controls but that is not represented to be for use in supporting or sustaining human life (or preventing impairment to health) and does not present an unreasonable risk of illness or injury.
- Class II devices are those that cannot be classified into Class I, because general controls are not sufficient by themselves to provide reasonable assurance of safety and effectiveness, but on which there is sufficient information to establish a special control to provide reasonable assurance. Originally, Class II called solely for performance standards. A performance standard might include provisions regarding the construction, components, ingredients, and properties of the device and its comparability with power systems; provisions for the testing of the device to ensure conformity to the standard; provisions for measurement of performance characteristics of the device; provisions making the device a “restricted device”; and special labeling requirements related to the installation, maintenance, operation, and use of the device. Since 1990, Class II devices have been subject to special controls, which may include performance standards, guidelines for the submission of clinical data in premarket notification submissions in accordance with Section 510(k), and other controls, such as compliance with an FDA guidance document.
- Class III devices are those that are represented for use in supporting or sustaining life (or preventing impairment of health) or create a potentially unreasonable risk of illness or injury, but which cannot be classified into Class I or Class II, because the general controls are inadequate to give reasonable assurance of safety and effectiveness and the available information is insufficient to establish a special control to provide the requisite assurance.

The Safe Medical Devices Act (SMDA) of 1990 permitted substantial equivalence to be established to marketed postamendment, in addition to preamendment, “predicate” devices, except for devices approved by PMA. Congress’s interpretation of substantial equivalence, as stated in the SMDA, is shown in Box S-2. The SMDA also gave the FDA authority to impose

BOX S-2
Definition of Substantial Equivalence in the
1990 Safe Medical Devices Act

A. For purposes of determinations of substantial equivalence . . . the term “substantially equivalent” or “substantial equivalence” means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that [FDA] by order has found that the device –

(i) has the same technological characteristics as the predicate device, or

(ii) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including clinical data if deemed necessary by [FDA], that demonstrates that the device is as safe and effective as a legally marketed device and (II) does not raise different questions of safety and efficacy than the predicate device.

B. For purposes of subparagraph (A), the term “different technological characteristics” means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.

on Class II devices, one or more special controls (which include a range of regulatory options), in addition to performance standards.¹

The Food and Drug Administration Modernization Act of 1997 eliminated the requirement for 510(k) clearance for most Class I and some Class II device types, narrowed the array of issues that the FDA may consider in a 510(k) review, and directed the FDA to limit, to the “least burdensome” level, the scientific evidence requested to determine substantial equivalence of devices that involved new technologies.

Today, the 510(k) clearance process is the primary pathway to market for Class II devices. More than 80% of 510(k)-cleared devices are categorized as Class II device types. Some Class I and Class III device types also are cleared through the 510(k) process.

In 2002, in an effort to address insufficient resources of the 510(k) and PMA programs, Congress passed legislation to create a 5-year user-fee program. The user-fee program was renewed in 2007 for another 5 years.

¹Special controls include performance standards, postmarket surveillance, patient registries, and guidelines for the submission of clinical data in premarket notification submissions in accordance with Section 510(k).

The 510(k) clearance process has become a major component of medical-device regulation in the United States. Thousands of devices are cleared via the 510(k) process each year—about one-third of devices entering the market. The remaining devices are exempt from any premarket review (67%) or enter the market by the PMA pathway (1%) or by other means such as the humanitarian-device exemption (1%). Because the FDA has not promulgated performance standards or special controls for the vast majority of types of Class II devices, and because when a special control applies it does not necessarily apply to all aspects or components of the device, the basis for market entry for Class II devices has been (and remains) demonstration of substantial equivalence to a predicate device.

In recent years, individuals and organizations have expressed concern that the 510(k) clearance process is neither making safe and effective devices available to patients nor promoting innovation in the medical-device industry. Several high-profile mass-media reports and consumer-protection groups have profiled recognized or potential problems with medical devices cleared through the 510(k) clearance process. The medical-device industry and some patients have asserted that the process has become too burdensome and is delaying or stalling the entry of important new medical devices to the market.

THE COMMITTEE'S TASK

The FDA asked the Institute of Medicine to review the 510(k) clearance process for medical devices and to answer two questions:

1. Does the current 510(k) clearance process optimally protect patients and promote innovation in support of public health?
2. If not, what legislative, regulatory, or administrative changes are recommended to optimally achieve the goals of the 510(k) clearance process?

CONCLUSIONS

In its approach to its task, the committee evaluated components of the 510(k) process and other relevant factors, including

- The legislative history of the 510(k) program.
- The 510(k) regulatory framework that resulted from legislation.
- How the 510(k) process fits into the larger medical-device regulatory framework. (The 510(k) clearance process is an integrated component of the larger medical-device regulatory framework. The

committee evaluated the 510(k) program in the context of this larger framework.)

- How the 510(k) process is implemented by the FDA.
- Available postmarket information on the safety and effectiveness of 510(k)-cleared devices.
- Other factors that affect medical-device regulation (for example, the process of innovation and the environment in which medical devices are developed and commercialized).

On the basis of its review and evaluation of legislative, regulatory, and administrative components of the 510(k) clearance process and other related components of medical-device regulation, the committee came to two major conclusions.

Conclusion 7-1 The 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices with some exceptions. The 510(k) process cannot be transformed into a pre-market evaluation of safety and effectiveness as long as the standard for clearance is substantial equivalence to any previously cleared device.

The 510(k) process is technically a classification mechanism by which a new device can be assigned to Class II and thereby enter the market without undergoing either the PMA process or the time-consuming formal device reclassification process. By law, the standard for classification and clearance is substantial equivalence to any predicate device already in Class II. The assessment of substantial equivalence does not require an independent demonstration that the new device provides a “reasonable assurance of safety and effectiveness,” as the statute requires for PMAs for new Class III devices. Rather, substantial equivalence requires a comparison of a new device to a legally marketed predicate that is, with few exceptions, either a preamendment device placed in Class II by the FDA based on reviews by outside advisory panels, a postamendment device that was originally approved as safe and effective by PMA and subsequently was reclassified into Class II, a postamendment device that was placed in Class II by the *de novo* review process based on a showing of safety and effectiveness, or a postamendment device that has been cleared through the 510(k) process as substantially equivalent to a device in one of the foregoing categories. In practice, most predicates fall within the first and last groups. According to the FDA and the Supreme Court, when the FDA finds a device substantially equivalent to a predicate device, the agency has not determined that the device is actually safe and effective; it has done no more than find that the

new device is as safe and effective as the predicate. Thus, a critical question is whether the predicate was found to be safe and effective.

The classification of preamendment devices did not include any evaluation of the safety or effectiveness of individual medical devices. The FDA created advisory panels to assist in the device classification process. These panels reviewed information on the risks posed by types of devices, including the potential risks resulting from a failure of lack of effectiveness, and recommended into which class the device type should be placed, in order to provide a reasonable assurance of safety and effectiveness. Neither the panels nor the FDA itself undertook an assessment of the clinical safety or effectiveness of individual devices during the original classification process. Thus, it is common for devices to be cleared through the 510(k) program by being found substantially equivalent to devices that were never individually evaluated for safety and effectiveness, either through the original device classification program or through the 510(k) process. Because the predicate device to which equivalence was established was itself generally not reviewed for safety and effectiveness, the committee found that clearance of a 510(k) submission was not a determination that the cleared device was safe or effective.

The 1990 SMDA permitted the FDA to require evidence of safety and effectiveness, including clinical studies, when necessary to determine whether a difference in technologic characteristics between a new device and its predicate renders the new device less safe or effective than the predicate or raises different questions of safety and effectiveness from the predicate. If, despite the change in technologic characteristics, the new device is as safe and effective as the predicate, it will be found substantially equivalent. Nearly all 510(k) submissions for devices that have new technologic characteristics receive a determination of substantial equivalence.

The committee found that available information on postmarket performance of devices does not provide sufficient information about potential harm or lack of effectiveness to be a useful source of data on the safety and effectiveness of marketed devices. The committee does not believe, however, that there is a public-health crisis related to unsafe or ineffective medical devices. Although the safety and effectiveness of individual preamendment Class II devices have not been systematically reviewed, their continued use in clinical practice provides at least a level of confidence in their safety and effectiveness.

Conclusion 7-2 Information that would allow an understanding of the extent to which the 510(k) clearance process either facilitates or inhibits innovation does not exist.

The committee believes that innovation is not just a change but a favorable change in the context of public health, and it defined innovation as improving the quality of, efficiency of, or access to health care. It is not necessary for a Class II device to be demonstrated to be innovative to be cleared for marketing. The FDA should not be the arbitrator of what constitutes innovation, nor should it seek to channel device development and premarket review toward agency-determined public-health priorities.

The regulatory process can facilitate innovation that improves public health by making safe and effective Class II medical devices available to consumers in a timely manner. The FDA's role in facilitating innovation in Class II medical devices through premarket review should be to create a regulatory framework that sets appropriate thresholds for bringing products to the market. Those thresholds should be stringent enough to satisfy the agency's objective of ensuring that marketed medical devices will be safe and effective throughout their life cycles but realistic enough to permit timely entry of new devices that may offer improvements over already marketed devices. Rather than be charged with *promoting* innovation, the committee believes that the FDA should seek to *facilitate* it.

To assess how innovation is affected by medical-device regulation, the committee studied the legislative history and implementation of the 510(k) process. It is unclear—and the committee argues that it is indeterminable, given current data—whether legislative, regulatory, and administrative changes over the past 35 years have had a positive or negative effect on innovation.

Several assessments of the 510(k) program have concluded that the FDA's implementation of the program—not the underlying process itself—has stifled innovation because of a lack of transparency and predictability, which has had an adverse effect on venture-capital investment in future medical-device development. Typical measures used in those assessments are the ease of premarket review and relative speed to market compared with the European Union premarket process. The committee, however, does not believe that such measures are surrogates for innovation.

The FDA has procedures for developing, adopting, and implementing guidance and standards. The agency, however, is persistently hindered in fully developing those materials by a lack of or limitations on human, fiscal, and technologic resources and capabilities. The lack of clear guidance affects the timeliness and consistency of 510(k) device submissions provided by industry and the ability of reviewers to evaluate them.

RECOMMENDATIONS

The committee does not believe that further investment in the 510(k) process is a wise use of the FDA's scarce resources and is not recommending

specific changes in the 510(k) clearance process itself. Instead, it believes that the FDA's resources would be put to better use in obtaining information needed to develop a new regulatory framework for Class II medical devices and addressing problems with other components of the medical-device regulatory framework. The committee recognizes that scarce resources in the FDA could affect its ability to implement the recommendations and, therefore, has directed the recommendations toward activities that are useful in both the short term and the long term to conserve scarce resources.

Designing a New Medical-Device Regulatory Framework

Recommendation 7-1 The Food and Drug Administration should obtain adequate information to inform the design of a new medical-device regulatory framework for Class II devices so that the current 510(k) process, in which the standard for clearance is substantial equivalence to previously cleared devices, can be replaced with an integrated premarket and postmarket regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle. Once adequate information is available to design an appropriate medical-device regulatory framework, Congress should enact legislation to do so.

The committee believes that a move away from the 510(k) clearance process should occur as soon as reasonably possible but recognizes that it will take time to obtain the information needed to design the new framework.

The new regulatory framework must be based on sound science and be developed in harmony with other components of the FDA's medical-device regulatory system. The committee does not believe that available information is adequate to inform the design of an appropriate framework.

The types of evidence necessary to demonstrate a reasonable assurance of safety and effectiveness according to the new framework should be carefully considered. It is beyond the committee's scope of work to detail those types of evidence. It may be possible, however, for the performance of comparative devices to be a component of the evidentiary materials supporting a claim of safety and effectiveness of Class II devices.

On the basis of its findings, the committee identified several topics to which the FDA should give particular consideration as it develops a new framework. A number of existing and emerging technologies (for example, combination products, software, nanotechnology, and medical robotics) merit detailed thought as part of the development of the new framework. The FDA should consider integrating some elements of the quality-system regulations, especially those related to design controls and product-release

criteria, into the premarket review process of the new framework to demonstrate that devices will perform as represented by their manufacturers. The FDA should also consider, as part of the new framework, including a more extensive review of device labeling and a system of tracking of labeling changes.

A comprehensive review of the successes and problems of device regulation over the past 35 years would better inform the FDA and Congress how to change the overall regulatory structure for devices. Finally, medical-device regulatory systems in other countries and jurisdictions should be evaluated to determine whether components of those systems could inform the design of the new regulatory framework in the United States.

The committee urges the FDA to create a regulatory framework that closely matches the ideal regulatory framework outlined by the committee. The attributes of the ideal framework are as follows (not presented in any priority order):

- The process should be based on sound science.
- The process should be clear, predictable, straightforward, and fair.
- The process should be self-sustaining and self-improving.
- The process should facilitate innovation that improves public health by making medical devices available in a timely manner and ensuring their safety and effectiveness throughout their life cycle.
- The process should apply relevant and appropriate regulatory authorities and standards throughout the life cycle of devices to ensure safety and effectiveness.
- The process should be risk-based.

FDA staff at all levels, the medical-device industry, consumers, health-care providers, payers, and Congress must play a role in the development of the proposed regulatory framework.

Postmarketing Surveillance

Robust postmarketing surveillance is particularly important for medical devices because devices often are used by small numbers of patients, so large premarket safety and effectiveness studies are not feasible. As noted above, the 510(k) clearance process is not a stand-alone program but a component of the larger medical-device regulatory framework. As part of that framework, the 510(k) program depends on the effectiveness of other regulatory components. The committee found substantial weakness in postmarketing surveillance of medical devices. The inadequate postmarketing surveillance systems, both those in the FDA and those that are privately funded, and the resulting lack of useful, consistent, and reliable data make it impossible to

draw confident conclusions about the performance of medical devices that are now on the market.

Recommendation 7-2 The Food and Drug Administration should develop and implement a comprehensive strategy to collect, analyze, and act on medical-device postmarket performance information.

The FDA should give priority to postmarketing surveillance as an invaluable investment in short-term and long-term oversight of medical-device safety and assessment of device effectiveness. Congress should support the capacity of the FDA's postmarketing surveillance programs by providing stable and adequate funding.

The FDA should develop a postmarketing surveillance strategy to meet the following objectives: providing performance information for use in the premarket review process, informing the development and use of postmarketing tools (that is, general and special controls²) to better manage the risk-benefit ratio throughout the life cycle of devices, and informing the design of a new regulatory framework.

Postmarket Regulatory Authorities³

When the FDA discovers violations of the law or products that pose unacceptable risks to consumers, it has a wide variety of authorities (or tools) available to try to remedy the situation and to sanction the violators. The committee found that the agency uses those authorities sparingly. The FDA reports that there are "important limitations" on the use of postmarket authorities, but does not describe them. The committee identified the procedural requirements that the FDA must fulfill to exercise the authorities, but the requirements do not in themselves appear to explain the agency's perception that there are limitations on its use of postmarket tools.

Recommendation 7-3 The Food and Drug Administration should review its postmarket regulatory authorities for medical devices to identify existing limitations on their use and to determine how the limitations can be addressed.

The appropriate use of postmarket regulatory authorities is an essential component of a successful medical-device regulatory program. The FDA should analyze barriers to efficient and effective use of the authorities and

²General controls include manufacturer registration, device listing, and good manufacturing practices. Special controls are described above.

³In this report, the phrase *regulatory authority* refers to the power that the legislature gives the FDA to enforce statutes.

identify means of mitigating them. If it is required, Congress should pass legislation to remove unnecessary barriers to the FDA's use of postmarket regulatory authorities.

A Modified De Novo Process

The de novo process is a mechanism by which the FDA can down-classify, to Class I or Class II, devices that have no predicates but are deemed to be of low to moderate risk. The process avoids having novel, low- to moderate-risk devices go through the PMA process. In the de novo process, a 510(k) submission for the device is sent to the FDA, which issues a determination of "not substantially equivalent" and indicates to the applicant that the device may be eligible for the de novo process. Special controls generally need to be developed for the device. The general and special controls must be sufficient to provide reasonable assurance of safety and effectiveness.

The de novo process offers a potential basis of a better regulatory model for premarket review of Class II devices. In its current state, however, the de novo process is time-consuming and difficult for both the FDA and manufacturers to navigate.

Recommendation 7-4 The Food and Drug Administration should investigate the viability of a modified de novo process as a mechanism for evaluating the safety and effectiveness of Class II devices.

A pilot program of a modified de novo process would allow the FDA to determine its feasibility as a replacement for the 510(k) clearance process. As part of a modified de novo process, the FDA should explore ways to expedite development of special controls, develop guidance, and adopt standards for devices. The agency also should consider expanded use of external expertise and preinvestigational device-exemption meetings with submitters and use of conditional clearances (such as postmarketing surveillance or use of registries) for devices on which there is little premarket performance information.

A Continuous Quality-Improvement Program

It is the committee's assessment that the FDA lacks a continuous quality-assurance process for regulation of medical devices. As a result, the FDA cannot effectively address new issues as they arise.

Recommendation 7-5 The Food and Drug Administration should develop and implement a program of continuous quality-improvement

to track regulatory decisions on medical devices, identify potential process improvements in the medical-device regulatory framework, and address emerging issues that affect decision-making.

The committee found evidence that the inadequate information technology and management infrastructure in the FDA affects not only the 510(k) program but also the agency's other programs for regulating medical devices. For example, because data systems are inadequate, the FDA does not have the ability to trace the history of 510(k) decisions. Prior 510(k) clearances are legally binding on the FDA when making 510(k)-clearance decisions. Thus, any unsafe or ineffective devices are embedded in the system and as both a legal and a practical matter may be used as predicates for new devices until the predicates are removed from the market. It may be difficult for the FDA to remove devices from the market because it has no systematic way to identify them. By developing a business model grounded in continuous quality-improvement, the FDA will be better able to identify problems with devices and develop the information and capacity to address them in a data-driven, transparent manner.

Facilitating Innovation in the Medical-Device Industry

The FDA's role in facilitating innovation with respect to Class II devices is to create and enforce a regulatory framework for which the threshold to market provides reasonable assurance that medical devices are safe and effective throughout their life cycle while permitting timely entry of new devices that may offer improvements over already marketed devices. The committee did not find assessments of how much and in what way (that is, facilitating or inhibiting) innovation is influenced by the 510(k) clearance process.

Recommendation 7-6 The Food and Drug Administration should commission an assessment to determine the effect of its regulatory process for Class II devices on facilitating or inhibiting innovation in the medical-device industry.

The recommended study should include various ways to measure innovation beyond "time to market" or the number of devices of a particular type on the market and instead focus on a broader understanding of the relationship among regulation, innovation, and patient health and safety throughout device life cycle.

Software

Manufacturers are increasingly using software in devices, software as devices, and software as a tool in producing devices. That trend is expected to continue. The committee found that current guidance on software validation is insufficient for preventing serious software-based device failures.

Recommendation 7-7 The Food and Drug Administration should develop procedures that ensure the safety and effectiveness of software used in devices, software used as devices, and software used as a tool in producing devices.

The FDA should develop a better understanding of the roles of software in medical devices, analyze its potential effects on the safety and effectiveness of the devices, and insist on evidence-based procedures that ensure device safety and effectiveness. Given the increasing use of software in devices and as devices (for example, medical device data systems), the integration in devices of commercial software not intended for use in medical devices, the increasing uncertainty introduced by device complexity, and potentially unsafe interactions with other software systems, the committee believes that the FDA should review and update its guidance on software validation.

Preamendment 510(k)-Eligible Class III Devices

After 35 years, the FDA has not completed the task of calling for PMAs for or reclassifying preamendment Class III device types. Until the FDA completes that task, those devices are allowed to enter the market through the 510(k) clearance process. Congress in 1990 directed the FDA to complete this task in a timely manner. Twenty-five Class III device types remain eligible to enter the market through the 510(k) process. The FDA has begun a five-step process to require PMAs or to down-classify those device types. As of April 2011, the FDA had assessed the risks and benefits associated with 21 device types (step 2 of the process) and had received and reviewed public comments on five device types (step 4 of the process). The agency has issued a final rule for one of the 26 device types. The committee recognizes the resource constraints that have prolonged the process, but it nevertheless urges the FDA to give high priority to completing the task.

Recommendation 7-8 The Food and Drug Administration should promptly call for PMA applications for or reclassify Class III devices that remain eligible for 510(k) clearance.

1

Introduction

The US Food and Drug Administration (FDA), through its Center for Devices and Radiological Health (CDRH), regulates medical devices and radiation-emitting products.¹ The 510(k) clearance process, also called premarket notification, has become a major component of the medical-device regulatory framework² in the United States. In passing the Medical Device Amendments of 1976, Congress intended the 510(k) process to be a short-term expedient to facilitate the agency's formidable task of classifying all marketed devices according to risk, reviewing high-risk medical devices on the market at that time for safety and effectiveness, and facilitating the entry of new devices until classification and review processes were in place. Until then, medical devices generally had not undergone premarket review³ by the FDA. The 510(k) clearance process was established to permit new medical devices to be brought to market by demonstrating only that they were substantially equivalent⁴ to already currently marketed devices, which were referred to as predicates.

In recent years, policy-makers, scientists, and others have expressed concern that the 510(k) clearance process is neither making safe and effec-

¹The FDA's Center for Biologics Evaluation and Research regulates some medical devices, which involve blood, cellular products, and tissues. The present report pertains only to medical devices under the jurisdiction of CDRH.

²In this report, the phrase *regulatory framework* is defined as including both premarket and postmarket activities. It covers the entire product life cycle of devices.

³In this report, *premarket review* refers to FDA oversight that occurs before devices enter the market. Premarket review of devices includes both the 510(k) clearance process and the premarket approval process.

⁴The concept of substantial equivalence is discussed in later chapters.

tive devices available to patients nor fostering innovation in the medical-device industry.⁵ In the past several years, that issue has received attention in the press because of recognized or potential problems with several devices that had been cleared through the 510(k) process, including an artificial hip (Meier, 2010), a patch for injured knees (Harris, 2010a; Mundy and Favole, 2009; Stein, 2010), surgical mesh (Bloomberg News, 2008), and medical-tubing connectors (Harris, 2010b; Shuren, 2010).

In September 2009, the FDA asked the Institute of Medicine (IOM) to review the 510(k) clearance process for medical devices and to answer two questions:

- Does the current 510(k) clearance process protect patients optimally and promote innovation in support of public health?
- If not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) clearance process optimally?

In response to the FDA's request, IOM appointed the Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process. This report summarizes the committee's review of the 510(k) clearance process, its conclusions on whether the process is protecting patients optimally and promoting innovation, and its recommendations.

This chapter provides a brief overview of medical devices and of the challenges associated with regulating them. It describes the general approach used by the committee to complete its challenging task and includes a discussion of changes that CDRH is making in the 510(k) program. The chapter ends with a roadmap for the rest of the report.

WHAT IS A MEDICAL DEVICE?

The Federal Food, Drug, and Cosmetic Act (FFDCA)⁶ defines a device as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is

- Recognized in the official National Formulary, or the US Pharmacopoeia, or any supplement to them,

⁵For example, letter from Representatives Henry A. Waxman, Bart Stupak, and Frank Pallone, Jr., Committee on Energy and Commerce, US House of Representatives, to Joshua M. Sharfstein, Principal Deputy Commissioner, US Food and Drug Administration (May 11, 2009); letter from Carmella Bocchino, America's Health Insurance Plans, to FDA, Docket FDA-2010-N-0054, Document FDA-2010-N-0054-0047 (March 19, 2010).

⁶Federal Food, Drug, and Cosmetic Act §201(h), 21 USC § 321(h) (2006).

- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

An enormous variety of medical devices are available to physicians, patients, and other consumers. As apparent from the FFDCA definition, medical devices can range from such simple tools as tongue depressors and bandages to such complex or life-saving equipment as pacemakers, cochlear implants, and heart–lung machines. Medical devices are used to diagnose, treat for, and prevent disease. They are used in healthcare facilities—such as hospitals, physicians’ offices, and nursing homes—and at home.

THE CHALLENGE OF REGULATING MEDICAL DEVICES

A number of actors—including medical-device companies, regulators (the FDA), payers (such as the Centers for Medicare and Medicaid Services and private health insurers), and consumers (healthcare providers, healthcare facilities, and patients)—are involved in bringing medical devices to market (IOM, 2010). Medical-device companies, which develop new devices and iterative versions of existing devices, expect a regulatory process that is reasonable, fair, and timely. The FDA seeks to protect and promote the public’s health by ensuring that safe and effective medical devices continue to be made available to consumers in a timely manner without unreasonable cost to industry. Payers and consumers expect that the regulatory process will provide reasonable assurance that marketed medical devices are safe and effective.

Congress, recognizing that devices are fundamentally different from drugs, crafted legislation to regulate devices according to a framework different from that used to regulate drugs. Devices and drugs differ in several ways. Devices tend to have shorter product life cycles than drugs. Incremental changes in devices are common, whereas a change in a drug alters its molecular structure and in effect creates a new drug. Drugs may be used by thousands or millions of consumers; but many devices are used by only a small number of patients, so large premarket randomized, controlled studies to detect rare events or small differences between products may not be feasible. The technology of medical devices changes rapidly, so long-term premarket studies to detect risks that emerge slowly are difficult or impossible. Although the committee reviewed some aspects of regulation

of drugs as part of its work, it acknowledged from the outset that because of profound differences between devices and drugs, different regulatory frameworks are required.

The committee, for purposes of its work, defined *safety*, *effectiveness*, and *innovation*, all terms used in the statement of task. The committee's understandings of the concepts of reasonable assurance of safety and of effectiveness are derived from the FFDCAs and Part 860 of the *Code of Federal Regulations*.⁷ A device is considered to provide reasonable assurance of safety when it can be determined, on the basis of valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use outweigh any probable risks. A device is considered to provide reasonable assurance of effectiveness when it can be determined, on the basis of valid scientific evidence, that use of the device for its intended uses under the conditions prescribed, recommended, or suggested in its labeling will provide clinically significant results. The committee believes that the device should provide results that are not just clinically significant but beneficial to patients. The committee also took into consideration the Agency for Healthcare Research and Quality (AHRQ) definition of effectiveness (AHRQ, 2011). AHRQ bases effectiveness on "whether a drug or other treatment works in real life. Effectiveness studies of drugs look at whether they work when they are used the way that most people take them. Effectiveness means that most people who have the disease would improve if they used the treatment." That definition applies to devices as well as to drugs. The committee took a broader view than the AHRQ definition. It recognizes that not all devices are used as therapeutics (for example, in vivo or in vitro diagnostic devices). In that circumstance, effectiveness could be based on whether the device provides information that contributes to medical decision-making. The committee also recognizes that not all device-based therapies are directed toward curative outcomes or an improvement in health status. They can be used to slow the progression of disease or stabilize chronic debilitating diseases. In such cases, effectiveness could be based on whether the device-based therapy produces some benefit relative to the natural history of the underlying disease. Effectiveness must be differentiated from efficacy, which AHRQ bases on "whether a drug or other treatment works under the best possible conditions [for example, a clinical trial]." It should be noted, therefore, that premarket clinical trials actually measure efficacy, whereas data derived from postmarketing surveillance (for example, in registries) measure effectiveness. A mandate to ensure effectiveness must by definition measure utility in a "real-world" environment.

⁷FFDCA § 513(a)(3), 21 USC § 360c(a)(3) (2006); 21 CFR § 860.7(e)(1).

Defining innovation is more challenging. Views on what constitutes innovation vary widely. Various types of changes in medical devices can be considered innovative, from truly novel changes to minor changes to changes that may not alter the functionality of a device but reduce its cost or extend its availability and thereby allow increased access. In the context of the present report, the committee defined innovation as something that improves the quality of, efficiency of, or access to healthcare. Class II devices do not need to be shown to be innovative to be cleared for marketing. Premarket regulation of moderate-risk devices can facilitate innovation that improves public health by making safe and effective devices available to consumers in a timely manner. More discussion of innovation is presented in Chapter 6.

THE COMMITTEE'S APPROACH TO ITS TASK

The committee's work involved gathering information, reviewing evidence, and formulating, deliberating on, and coming to consensus on findings, conclusions, and recommendations. This report summarizes the committee's work and presents its conclusions and recommendations.

The committee met in person six times from March 2010 to January 2011. At the March meeting, the committee held a public session to discuss its charge with CDRH, the sponsor of its study; in June and July 2010, it hosted public workshops. In closed session, the committee planned the workshops, reviewed evidence, and deliberated and reached consensus on its findings, conclusions, and recommendations. The committee considered many possible avenues as it responded to its task. The conclusions and recommendations included in this report were selected on the basis of the strength of the evidence and the committee members' expert judgment.

The committee found that it was not possible to review the 510(k) clearance process in isolation from other components of medical-device regulation and oversight. Therefore, although some of the topics included in the present report are not explicitly parts of the 510(k) clearance process, they are related to the FDA's ability to identify and address safety and effectiveness concerns about medical devices that emerge throughout their life cycles.

Data-Collection Efforts

The committee took a multipronged approach to collecting information. It hosted two public workshops, in June and July 2010, on a number of topics related to medical-device regulation. Topics covered during the June workshop included the legislative history of the 510(k) clearance process and its current structure, the structure of the medical-device industry and how it is affected by regulation, the regulation of medical devices globally,

and consumer concerns. Members of the public were invited to give comments. The July workshop dealt with postmarketing surveillance of and reporting of adverse events related to medical devices and with several other topics of interest to the committee, such as risks associated with software in medical devices. The committee commissioned four papers, which were presented at the workshops. Summaries of the presentations and discussions at the workshops have been published (IOM, 2010, 2011), and the commissioned papers are included in the workshop summaries.

Other means of information-gathering included extensive searches of the medical, scientific, and legal literature, review of information on innovation, review of FDA docket related to the CDRH internal review of the 510(k) clearance process, and review of CDRH's *Preliminary Internal Evaluations, Volumes 1 and 2* and other government reports, such as reports from the Government Accountability Office (GAO, 2009a, 2009b, 2009c, 2009d) and the Department of Health and Human Services Office of the Inspector General (OIG, 2009). CDRH responded promptly to the committee's many requests for information on the center's policies and procedures. Experts in the US and global medical-device field were contacted for additional information. And members of the public were encouraged to submit comments to the committee during the study process; the committee received and reviewed a number of such comments.

Limitations of Data-Collection Efforts

Limitations of the committee's data-collection activities affected the committee's ability to assess the quality of both the 510(k) submissions and CDRH's reviews of those submissions systematically. Because of limitations in the types of information captured in CDRH's databases, the committee could not review systematically such information as the types of data (for example, clinical data and bench-testing data) included in 510(k) submissions. The limitations in the FDA's information-technology systems are discussed further in Chapters 3 and 4.

The committee also considered conducting a systematic file review of 510(k) submissions and CDRH reviews. However, because of FDA statutory and regulatory protections for 510(k) submitter proprietary information, the committee was not able to review complete 510(k) submissions. As a result, a comprehensive file review of 510(k) submissions was not conducted. The committee was able to review several redacted 510(k) submissions supplied by CDRH. The committee also used information from government organizations (for example, GAO) and CDRH (for its internal preliminary evaluations) that had access to complete 510(k) submissions, CDRH's reviews, and other information. The committee found those analyses to be methodologically sound and used them as part of its evidence base.

ATTRIBUTES OF AN IDEAL MEDICAL- DEVICE REGULATORY SYSTEM

To be able to determine whether the 510(k) clearance process is optimally protecting patients and promoting innovation in support of public health, the committee first had to define the attributes of an ideal medical-device regulatory system. It started by defining two goals of medical-device regulation: to provide reasonable assurance that marketed devices, throughout their life cycles, are safe and effective according to current standards for the clinical indication at the time of use and to facilitate innovation by allowing prompt access of devices to the market. The committee next developed a list of six attributes, which are presented in Box 1-1. The attributes are not presented in any priority order.

The committee defined the attributes as follows. A medical-device regulatory system that is based on sound science uses appropriate scientific methods and evolving, state-of-the-art evidentiary standards; is data-driven; and provides for linkage of premarket and postmarketing information. A clear, predictable, straightforward, and fair regulatory system is accessible, responsive, transparent, reproducible, efficient (for example, it does not incur unnecessary costs or time), and credible; and it has conflict-resolution policies in place. A self-sustaining and self-improving (that is, robust) regulatory system uses continuous quality improvement and ensures the integrity of data and decision-making. A process that facilitates innovation is adaptable so that emerging technologies and policies can be incorporated and unforeseen circumstances can be addressed. The use of appropriate regulatory standards and authorities throughout a device's life cycle should

BOX 1-1

Attributes of an Ideal Medical-Device Regulatory System

- The process should be based on sound science.
- The process should be clear, predictable, straightforward, and fair.
- The process should be self-sustaining and self-improving.
- The process should facilitate innovation that improves public health by making medical devices available in a timely manner and ensuring their safety and effectiveness throughout their life cycle.
- The process should use relevant and appropriate regulatory authorities and standards throughout the life cycle of devices to ensure safety and effectiveness.
- The process should be risk-based.

include risk-based premarket reviews, credible and continuous postmarketing surveillance, and performance-based criteria that meet current clinical standards for continued availability of products demonstrated to be safe and effective. Finally, the process should incorporate risk-benefit analyses and flexible risk-mitigation strategies (for example, devices can be made available with special controls based on associated risks). Data and experience gathered at each stage of the product life cycle are used to inform other stages. Data collection from postmarketing surveillance should inform premarket review of new or modified devices.

The committee recognizes that no premarket regulatory system for medical devices can guarantee that all devices are completely safe and effective. That would set an impossible threshold. Any regulatory system must balance medical devices' risks and their potential public-health benefits. Given that a perfect premarket regulatory system is unrealistic, it is essential to have effective postmarket oversight of medical devices.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH ACTIVITIES RELATED TO THE 510(K) PROCESS

The 510(k) process has undergone substantial changes since its inception in 1976, and it continues to evolve. In addition to commissioning the present report, CDRH conducted an internal review of the 510(k) clearance process during 2009–2010. To carry out its review, it appointed an internal working group and charged it “to evaluate the 510(k) program and explore actions CDRH could take to enhance our 510(k) decision making.” The center’s findings and recommendations from that review were published in *CDRH Preliminary Internal Evaluations—Volume 1: 510(k) Working Group Preliminary Report and Recommendations* in August 2010 (FDA, 2010a). The focus was to be on actions that could be initiated in the short term without changes in existing statutory authority.

The working group, through the efforts of 10 subgroups, gathered information from CDRH staff at various levels (for example, reviewers and managers). It also queried internal databases and analyzed the data. And it sought input from stakeholders, such as medical-industry and patient representatives, through requests for public comments and several public meetings.

CDRH’s report offered seven major preliminary findings and recommendations were included in CDRH’s report in three categories: a rational, well-defined, and consistently interpreted review standard; well-informed decision-making; and continuous quality assurance. Those findings and recommendations are presented in Box 1-2.

At the same time that CDRH released *CDRH Preliminary Internal Evaluations—Volume I: 510(k) Working Group Preliminary Report and*

Recommendations, it released a second report, *CDRH Preliminary Internal Evaluations—Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations*. *Volume II* contains findings and recommendations in three major categories: enhancing CDRH's scientific knowledge base, applying a predictable approach to determine the appropriate response to new science, and promptly communicating current or evolving thinking to all affected parties (FDA, 2010b). Although this volume is not directly related to the 510(k) clearance process, it contains information that has the potential to affect the process. The committee reviewed both volumes as part of its evidence base.

After releasing its preliminary internal evaluations, CDRH published a notice in the *Federal Register* to request public comments on them. In January 2011, CDRH announced that it was moving forward with several of its recommendations (FDA, 2011). Twenty-five actions are scheduled to take place in 2011. Specific steps include

- Streamlining the review process for innovative, lower-risk products.
- Publishing guidance for industry to clarify when clinical data should be submitted to increase predictability and transparency.
- Developing a network of external experts who can use their knowledge and experience to help the agency to address important scientific issues regarding new medical-device technologies.
- Establishing a new Center Science Council of senior FDA experts in CDRH to ensure more timely and consistent science-based decision-making.
- Establishing a public database of important device information, such as medical-device labeling and summaries of the basis of FDA's decisions to clear specific devices.
- Requiring a brief description of scientific information known to manufacturers regarding the safety and effectiveness of select higher-risk devices case by case basis through device-specific guidance.

CDRH identified seven recommendations that it determined, on the basis of comments received from members of the public, raised substantial stakeholder concerns. The issues addressed by those recommendations are

- Defining the scope and grounds for CDRH to exercise its authority to rescind a 510(k) clearance fully or partially.
- Seeking greater authority to require postmarket surveillance studies as a condition of clearance for some devices.
- Developing guidance defining Class IIb devices for which clinical information, manufacturing information, or, potentially, additional

BOX 1-2**CDRH's Preliminary Finding and Recommendations from Its Review of the 510(k) Clearance Process****A Rational, Well-Defined, and Consistently Interpreted Review Standard**

Finding 1: There is insufficient clarity with respect to pivotal terms in the definition of “substantial equivalence.”

Recommendation 1: CDRH should clarify the meaning of “substantial equivalence” through guidance and training for reviewers, managers, and industry.

Finding 2: CDRH's current practice allows for the use of some types of predicates that may not be appropriate.

Recommendation 2: CDRH should explore the development of guidance and regulation to provide greater assurance that any comparison of a new device to a predicate is valid and well-reasoned.

Finding 3: Although there exists an alternative regulatory pathway for devices that lack a clear predicate but whose risks do not warrant Class III controls (i.e., the process for Evaluation of Automatic Class III Designation, also known as the *de novo* classification process), this pathway, as currently implemented, is inefficient and has not been utilized optimally across the Center.

Recommendation 3: CDRH should reform its implementation of the *de novo* classification process to provide a practical, risk-based option that affords an appropriate level of review and regulatory control for eligible devices.

Well-Informed Decision Making

Finding 4: It is challenging for CDRH to obtain, in an efficient and predictable manner, the information it needs to make well-supported

evaluation in the postmarket setting would typically be necessary to support a determination of substantial equivalence.

- Clarifying when a device should no longer be available for use as a predicate.
- Consolidating the concepts of “indications for use” and “intended use” into a single term, “intended use.”
- Requiring each 510(k) submitter to keep at least one unit of the device that is under review available for CDRH to access on request.
- Pursuing a statutory amendment that would provide the agency with

premarket decisions and assure that each new or modified 510(k) device is substantially equivalent to a valid predicate.

Recommendation 4: CDRH should take steps through guidance and regulation to facilitate the efficient submission of high-quality 510(k) device information, in part by better clarifying and more effectively communicating its evidentiary expectations through the creation, via guidance, of a new “Class IIb” device subset.

Finding 5: Limitations in CDRH’s information technology and knowledge management infrastructure and tools make it challenging for Center staff and 510(k) submitters to access meaningful medical device information that would support better-informed and more predictable decision-making.

Recommendation 5: CDRH should take steps to enhance its internal and public information systems and databases to provide easier access to more complete information about 510(k) devices and previous clearance decisions.

Continuous Quality-Assurance

Finding 6: Variations in the expertise, experience, and training of reviewers and managers, including third-party reviewers, may contribute to inconsistency or uncertainty in 510(k) decision-making.

Recommendation 6: CDRH should enhance training, professional development, and knowledge-sharing among reviewers and managers, in order to support consistent, high-quality 510(k) reviews.

Finding 7: CDRH does not currently have an adequate mechanism to regularly assess the quality, consistency, and effectiveness of the 510(k) program.

Recommendation 7: CDRH should enhance its systems and program metrics to support continuous quality-assurance.

SOURCE: FDA, 2010b.

the express authority to consider an off-label use when determining the “intended use” of a device.

In its announcement, CDRH stated that it will “give the IOM an opportunity to provide feedback on selected recommendations should they decide to address these recommendations in their report” (FDA, 2011). CDRH’s announcement came toward the end of the committee’s work. Because of time constraints, the committee was unable to study fully the seven recommendations that CDRH referred to the committee. The committee did,

however, address many of the broader issues related to those recommendations in this report.

ORGANIZATION OF THE REPORT

Chapters 2–6 of this report summarize the committee's review of the evidence and lay out the logic for how it came to its conclusions and recommendations. Chapter 2 provides a brief history of federal legislation and regulation of medical devices, which has undergone many changes since devices were first regulated in 1938. Chapter 3 reviews how medical devices in general are regulated in the United States. Chapter 4 explores the 510(k) process in depth. Postmarketing surveillance is covered in Chapter 5. Chapter 6 discusses the environment within which medical devices are developed and how advancing technology is affecting how they are regulated. Finally, Chapter 7 contains the committee's conclusions and recommendations. The report has two appendixes. Readers who want a fuller understanding of federal legislation and regulation of medical devices are encouraged to read Appendix A. Appendix B contains biographic information on the committee members.

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2

Key Medical-Device Legislative and Regulatory Actions

Regulation of medical devices began in 1938 and reflected the technologically relatively simple devices then on the market. By the 1970s, the framework was no longer adequate or flexible enough to deal with the wide array of device types, the increasing sophistication of many technologies, and the occasional public-health disasters associated with a few devices. In 1976, Congress replaced the 1938 structure with a comprehensive system. As with most major new laws, refinements were needed, and in 1990 and 1997, Congress passed sets of substantial changes in the 1976 statute. Those three enactments make up the present framework.

The ability of the Food and Drug Administration (FDA) to carry out the directives of Congress has been constrained by chronically inadequate appropriations to the agency (FDA Science Board, 2007; GAO, 1983, 1989, 1992, 1995, 1996, 1997, 2009a; OTA, 1984).¹ In 2002 and 2007, Congress passed legislation that authorized the agency to charge the device industry user fees to expand premarket-review capacity. The user-fee legislation did not change the statutory structure, but it did require that the FDA meet performance goals.

This chapter will briefly review that history. Appendix A contains an extensive chronologic inventory of legislative enactments and Congressional examination of the implementation of the device laws.

¹H.R. REP. NO. 101-808, at 13 (1990); *see also* S. REP. NO. 101-513, at 14-15 (1990).

THE 1938 ACT

The original FDA statute, the Pure Food and Drug Act of 1906, did not cover medical devices. When Congress replaced it with the Federal Food, Drug, and Cosmetic Act of 1938 (FFDCA), it extended the law to medical devices, but for all intents and purposes devices were treated as drugs, and the definitions of the two categories overlapped. The overlap enabled the FDA, after a change in the drug law in 1962, to impose rigorous premarket approval of some products that today would be deemed devices.

In the 1960s, Presidents Kennedy, Johnson, and Nixon all called for new regulatory legislation specific to medical devices. By the early 1970s, several high-profile public-health problems with medical devices had led to political momentum for a device statute.²

THE 1976 ACT

The Medical Device Amendments of 1976 established an elaborate and detailed scheme, more than doubling the length of the FFDCA.³ After differentiating drugs from devices, the law created a broad array of authorities for the FDA to regulate devices after they had entered the marketplace. Moreover, in contrast with the US drug laws of the time, Congress limited premarket approval to only a small universe of devices. Where the drug law generally treated all drugs alike, the new device amendments created three categories of devices that were based on the risks presented and the ability of postmarketing controls to manage them. Only the highest-risk category would require agency review and approval as a precondition for commercial sale and routine medical use. The other two categories would be subject not to a rigorous review but merely to a requirement that the manufacturer of a device in one of the categories notify the FDA, at least 90 days before commencing marketing, of its intent to distribute the product commercially. That requirement was set forth in Section 510(k) of the FFDCA and thus is called a 510(k) notification.

The new law directed the FDA to categorize the device types in the universe of devices on the market when the 1976 law was enacted (so-called preamendment devices) into three categories—called Class I, Class II, and Class III—on the basis of the definitions that Congress adopted. Thereafter, under the statute, a device type could be transferred from one class to another on the basis of new information showing that it would now be more appropriately assigned to a different class. The criteria for the three classes were stated in the 1976 law as follows:

²H.R. REP. NO. 94-853, at 8 (1976).

³Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (hereinafter MDA).

- A Class I device is one of which the general postmarketing controls would be sufficient to provide reasonable assurance of safety and effectiveness. Class I can also include any device on which there is insufficient information to judge the adequacy of the controls but that is not represented as being for use in supporting or sustaining human life (or in preventing impairment of health) and does not present an unreasonable risk of illness or injury.⁴
- A Class II device is one that cannot be placed into Class I, because the general controls are not sufficient by themselves to provide reasonable assurance of safety and effectiveness but on which there is sufficient information to establish a performance standard to provide reasonable assurance. A performance standard might include provisions regarding the construction, components, ingredients, and properties of the device and its compatibility with power systems; provisions for the testing of the device to ensure conformity with the standard; provisions for measurement of performance characteristics of the device; provisions making the device a “restricted device”; and special labeling requirements related to the installation, maintenance, operation, and use of the device.⁵
- A Class III device is one that is represented as being for use in supporting or sustaining life (or in preventing impairment of health) or that creates a potential unreasonable risk of illness or injury and that cannot be placed into Class I or Class II, because the general controls are inadequate to give reasonable assurance of safety and effectiveness and because there is not sufficient information to establish a performance standard to provide the requisite assurance.⁶

Congress directed that the safety and effectiveness of a device were to be determined with respect to the persons for whose use the device is intended, with respect to the conditions of use in the labeling of the device, and by “weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.”⁷

The classification of preamendment devices did not include any evaluation of the safety or effectiveness of the individual medical devices. The FDA created advisory panels to assist in the device classification process. These panels reviewed information on the risks posed by types of devices, including the potential risks resulting from a failure of lack of effectiveness, and recommended into which class the device type should be placed, in order to provide a reasonable assurance of safety and effectiveness. Neither the

⁴FFDCA § 513(a)(1)(A), 90 Stat. 540 (1976) (subsequently amended).

⁵FFDCA § 513(a)(1)(B), 90 Stat. 541 (1976) (subsequently amended).

⁶FFDCA § 513(a)(1)(C), 90 Stat. 541 (1976) (subsequently amended).

⁷FFDCA § 513(a)(2), 21 USC § 360c(a)(2) (2006).

panels nor the FDA itself undertook an assessment of the clinical safety or effectiveness of individual devices during the classification process. Once a device type was assigned to Class III, the statute directed the FDA to promulgate a regulation calling for manufacturers of devices of that type to submit a premarket approval (PMA) application. The agency would then (and only then) undertake a review of the safety and effectiveness of the specific devices. For device types placed into Class I or Class II, there was no mechanism for the systematic post-classification review of safety and effectiveness. Congress envisioned instead that the agency would use its postmarketing tools to identify and address issues of lack of safety or lack of effectiveness case by case. Thus, preamendment devices in Class I and II were never subjected to a comprehensive FDA evaluation for safety or effectiveness. The classification process was not completed until 1988.

Finding 2-1 The safety and effectiveness of individual preamendment Class II medical devices has not been systematically reviewed. Continued use in clinical practice, however, provides at least a level of confidence in the safety and effectiveness of preamendment Class II medical devices still on the market.

In creating the new system, Congress also had to address how devices that were not on the market when the law was passed (so-called postamendment devices) could get onto the market. First, it concluded that if a new device were “substantially equivalent” to a preamendment device, it could enter the market on the same terms and conditions as the preamendment device. In other words, if the preamendment device had been placed into Class III, the substantially equivalent postamendment device would be in Class III and subject to PMA review when the FDA called for the PMA application for the preamendment device. If the preamendment device were placed into Class I or Class II, the substantially equivalent postamendment device would be permitted into the market subject to whatever controls or performance standards were applicable to the preamendment device. If the preamendment device had not yet been classified, the substantially equivalent postamendment device could come onto the market and be placed into the same class as the preamendment device when it was classified. When a manufacturer proposed to introduce a new (postamendment) device, including a modification of a preamendment device, it submitted a 510(k) notice identifying the preamendment device to which substantial equivalence was claimed and the supporting evidence, if needed or requested by FDA.

Second, Congress said that if the postamendment device were not “substantially equivalent” to any preamendment device, it would be automatically placed into Class III. To enter the market, the manufacturer would have

to obtain approval of a PMA application or successfully get the agency to reclassify the device into Class I or Class II.

Finding 2-2 The 510(k) clearance process was not designed in 1976 to evaluate the safety and effectiveness of new medical devices but only to assess their similarity to preamendment devices.

Congress did not define substantial equivalence in the 1976 amendments, and the legislative history contains a one-paragraph discussion that is, at best, ambiguous (FDA, 2010). Because of resource limitations, the FDA tended to find that postamendment devices were substantially equivalent to preamendment devices. To rule otherwise would increase the need for personnel to review PMA applications or to reclassify postamendment devices down from Class III, and both would have been labor-intensive activities. Furthermore, as time passed after 1976, the FDA adopted a practice of permitting a chain of devices to link a new postamendment device to earlier postamendment devices that ultimately could be traced back to a preamendment device; that is, Device A might be found substantially equivalent to Device B, which had been found equivalent to Device C, which had been found equivalent to Device D, and so on back to a preamendment device (FDA, 2010). The effect of those actions was that the 510(k) process evolved into a system that tended to find substantial equivalence far more often than nonequivalence.⁸ Between fiscal years 1976 and 2009, only 1–4% of 510(k) notifications submitted annually were found by the FDA to be not substantially equivalent (FDA, 2010, p. 39; GAO, 1997, p. 7; OTA, 1984, p. 104).

Finally, the resource constraints delayed the promulgation of regulations calling for PMA applications for preamendment Class III devices and establishing performance standards for Class II devices.⁹ Until those two steps occurred, Class II and Class III devices were subject to the same standard for market entry as Class I devices: demonstration of substantial equivalence to a preamendment device.

⁸Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 344 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

⁹1976 MDA § 514 (b)-(e) (removed by the Safe Medical Devices Act of 1990, Pub. L. No. 101-629 § 6(a)(2), 104 Stat. 4511, 4519-20 (1990) [hereinafter SMDA]); FFDCA § 515(b), 21 USC § 360e(b) (2006).

THE 1990 ACT

After a long series of investigations and hearings by Congress—through its committees, the Government Accountability Office (then called the General Accounting Office), and the Office of Technology Assessment—Congress passed the Safe Medical Devices Act of 1990. The goal was to address deficiencies that Congress identified in the 1976 law.¹⁰

Congress was clearly unhappy with the almost complete lack of progress in bringing all Class III devices into the PMA application system. To reduce that workload, the new law authorized the FDA to reclassify Class III devices that no longer warranted being in this category. For devices that remained in Class III, Congress directed the FDA to set a schedule—no later than December 1996—for promulgating the regulations needed to require submission of PMA applications. No final deadline for completing the process was set, however. (As of April 2011, it was not finished.)

For Class II devices, the new law addressed the FDA's failure to establish performance standards. Congress broadened the scope of the FDA's authority so that requirements or restrictions (called special controls) in addition to performance standards could be imposed; it made the imposition of special controls discretionary rather than mandatory; and it simplified the process by which performance standards could be established.

Congress also added new postmarketing tools to the agency's portfolio, underscoring the belief that premarket clearance would never be sufficient to protect public health.

With respect to the 510(k) process specifically, Congress adopted the more liberal interpretation of substantial equivalence that the FDA had been applying during the previous decade and thereby eliminated a fear that a court might declare that interpretation to violate the 1976 act. The agency, for example, had decided that a rigid reading of equivalence would not permit product improvements in safety and effectiveness; instead, a postamendment device could be determined to be substantially equivalent to another device even though it was claimed to be safer or more effective than the predicate with which it claimed comparability.¹¹ The standard applied was one of "noninferiority"; that is, the new device had to be "as safe and effective" as the reference device and did "not raise different questions of safety and effectiveness" from the reference device. (The FDA added a gloss on the interpretation of the latter criterion, saying that a new device could

¹⁰H.R. REP. NO. 101-808, at 13 (1990); *see also* S. REP. NO. 101-513, at 14-15 (1990).

¹¹Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 336-47 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

be cleared by the 510(k) process if it did not “raise new types of questions of safety and effectiveness” [IOM, 2010, p. 11].)

In addition, the new law permitted the establishment of equivalence to marketed preamendment or postamendment devices, called predicate devices, with the exception of devices approved by PMA. That change eliminated the need ever to construct a chain of 510(k) clearances back to a pre-1976 device. The only products that could not be considered as predicates were ones that had been removed from the market by order of the FDA or a federal court.

Finding 2-3 A 510(k) decision made by the FDA creates a precedent that is legally binding on the agency unless it has rescinded the decision or has barred the device covered by that decision from the market through other legal actions.

The relationship between the 510(k) process and innovation changed slightly in 1990. The 1976 law, literally read, would preclude a manufacturer’s use of the 510(k) process for a device that the company claimed would be safer and more effective than the preamendment device; changes that raised any issue of safety or effectiveness were (in theory, at least) to go through the PMA process instead. Moreover, from a narrow legal standpoint, successful compliance with the 510(k) process allowed a manufacturer only to market the covered device. Unlike laws that create a period in which a company has exclusive rights to sell a product (for example, under a patent or data-exclusivity provision), 510(k) established no special benefit for the first manufacturer to bring a certain device to market. Two companies could submit 510(k)s for competing products, each based on substantial equivalence to the same preamendment device, and each could be cleared without regard to the other.

In 1990, in ratifying the FDA interpretation of the substantial-equivalence standard as a noninferiority test and permitting clearance of products that did not raise different safety or effectiveness questions, Congress recognized that many innovative developments could be cleared with the 510(k) process and thus avoid the more burdensome PMA system. By eliminating the theoretical requirement of being able to trace a lineage back to a preamendment device, the 1990 law permitted comparisons with newer, more innovative state-of-the-art products.

In contrast, the 1990 legislation did not compel any manufacturer to evolve with the state of the art. As long as the submitter could find any lawfully marketed device to which it could successfully claim substantial equivalence, the agency would have to clear the 510(k) notification. Moreover, the FDA was not given any mandate to consider whether a proposed device under a 510(k) notification was in fact innovative. A fair reading

of the statutory scheme is that the FDA was to facilitate the clearance of new products that did not raise novel questions of safety and effectiveness, whether or not the product was an innovation. Presumably, the more efficiently and expeditiously Class I and Class II products were cleared, the more likely it would be that innovative products would reach the market.

Finding 2-4 The 510(k) clearance process was not designed to reward, recognize, or encourage innovation. At most, promotion of innovation was a byproduct of a process that, by minimizing unnecessary regulatory burdens, facilitated the entry into the market of new devices that did not raise novel questions of safety or effectiveness.

The definition of “substantial equivalence” used by the FDA in the 1980s and ratified by Congress in 1990 also permitted the FDA to require evidence of safety and effectiveness, including clinical studies, when necessary to determine whether a difference in technologic characteristics between the new device and its predicate rendered the new device less safe or effective than the predicate or raised different questions of safety and effectiveness from the predicate. This situation is the only one in which the FDA can consider the safety and effectiveness of a device as part of the 510(k) process. If, despite the change in technologic characteristics, the new device was as safe and effective as the predicate, it would be found to be substantially equivalent. About 15% of Class II and Class III 510(k) submissions for which the FDA reached a determination of substantial equivalence or nonsubstantial equivalence in FY 2005–2007 had new technologic characteristics (GAO, 2009b). Some 99.5% received a determination of substantially equivalent.

Because the assessment of substantial equivalence generally did not require evidence of safety or effectiveness of a device and because a preamendment device to which equivalence was established was not itself specifically reviewed for safety or effectiveness, the FDA made clear from the outset that clearance of a 510(k) notification was not a determination that the cleared device was safe or effective. That position was reiterated by the agency numerous times (OTA, 1984, p.128).¹² The US Supreme Court accepted this interpretation in a 1996 opinion (*Medtronic, Inc. v. Lohr*, 518 U.S. 470). In that opinion, the Court quoted favorably a critic of the 510(k) process:

¹²Memorandum Re: Internal Control Weaknesses in the Food and Drug Administration's Medical Device 510(k) Review Process, from the HHS inspector general to the HHS assistant secretary for health (July 5, 1990) 1, fn. 1; Brief for the United States as Amicus Curiae Supporting Respondents/Cross-Petitioners 19-20, *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) (No. 95-754) (some internal citations omitted).

Substantial equivalence determinations provide little protection to the public. These determinations simply compare a post-1976 device to a pre-1976 device to ascertain whether the latter is no more dangerous and no less effective than the earlier device. If the earlier device poses a severe risk or is ineffective, then the latter device may also be risky or ineffective.¹³

Finding 2-5 With limited exceptions, a determination by the FDA that one device is “substantially equivalent” to another device does not reflect an FDA evaluation of the safety or effectiveness of either device.

THE 1997 ACT

The Food and Drug Administration Modernization Act (FDAMA) was enacted by Congress in 1997. Congress had concluded that the FDA regulatory system was not keeping pace with medical innovation. “In a number of cases, for both 510(k)-cleared and PMA products, increased requirements that are burdensome, expensive, and time-consuming have delayed patients’ access to promising new devices.”¹⁴ In general, FDAMA restricted the agency’s authorities and eased the burdens on manufacturers seeking 510(k) clearance.¹⁵ The law specifically instructed the FDA to consider the extent to which postmarketing controls might expedite the preclearance process.

Congress eliminated the requirement for 510(k) notifications for most new Class I devices and some Class II devices to permit the FDA to concentrate its resources on higher-risk devices. The act imposed various constraints on the scope of review of 510(k) submissions so that the agency in general could no longer consider as grounds for a nonsubstantially equivalent determination other potential off-label uses of a proposed device¹⁶ or whether a manufacturer was in compliance with regulations pertaining to good manufacturing practices.¹⁷ Congress also directed that when a proposed new device included a change in technology such that the FDA had to determine whether the device was as safe and effective as its predicate, the FDA was not to request any evidence beyond the “least burdensome” means to demonstrate equivalence.¹⁸ Nothing in the legislative history of the

¹³Lohr, 518 U.S. at 493-94 (citations omitted).

¹⁴H.R. REP. NO. 105-307, at 13 (1997).

¹⁵Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

¹⁶The FDA may add labeling statements cautioning about specific foreseeable off-label uses. FFDCa § 513(i)(1)(E), 21 USC § 360e(i)(1)(E) (2006).

¹⁷The FDA may refuse to clear a 510(k) submission if it finds a substantial likelihood that noncompliance will “potentially present a serious risk to human health.” FFDCa § 513(f)(5), 21 USC § 360c(f)(5) (2006).

¹⁸FFDCa § 513(i)(1)(D), 21 USC § 360c(i)(1)(D) (2006).

1997 Act suggests that Congress disagreed with the Supreme Court's 1996 opinion that clearance of a 510(k) notification was not a determination that the cleared device was safe or effective.

The legislation also limited the application of some postmarketing tools to Class II and Class III devices and eased reporting requirements for adverse medical events.

Finding 2-6 The 510(k) clearance process has evolved from 1976 to the present through administrative and legislative changes, narrowing the array of issues that the FDA may consider in a 510(k) review and limiting the type of evidence that the FDA could require. Over 35 years, there has been a high frequency of finding substantial equivalence.

The PMA application has always been perceived as more onerous to manufacturers. As the 510(k) process was modified to facilitate clearance of new and improved products, the disincentives accompanying the PMA application became more apparent.

Finding 2-7 The gap in relative burdens on manufacturers between the 510(k) process and the PMA process created by the 1976 law has been maintained by administrative and legislative changes, which have encouraged preferential use of the 510(k) process.

THE 2002 AND 2007 ACTS

After years of insufficient resources for the PMA and 510(k) clearance processes (FDA Science Board, 2007; GAO, 1983, 1989, 1992, 1995, 1996, 1997, 2009a; OTA, 1984). Congress enacted a 5-year user-fee program in 2002 and renewed it in 2007. The enactments did not make fundamental changes in the regulatory framework. They did, however, provide supplemental funding for the FDA to use in reviewing of 510(k) submissions and PMA applications. Every establishment in which a device is manufactured must pay a fee with its required annual registration of names and places of business. Fees also must accompany each 510(k) submission, each original PMA application, each PMA supplement, and some other applications. The fees may be used only to support review activities, not other Center for Devices and Radiological Health (CDRH) operations, such as postmarketing safety monitoring and enforcement activities.

User fees are required only if two basic conditions are met. First, Congress must continue to appropriate a level of funding for CDRH review activities. The user fees are intended to augment, not replace, general revenues from taxes. The FDA may not collect user fees if public funding

falls below a specified level (calculated with a complex formula). Second, the agency must meet performance standards (such as completing reviews on at least 90% of all 510(k) notifications within 90 days of submission). The standards are established in correspondence between the Department of Health and Human Services and Congress.

The FDA is increasingly dependent on user-fee revenues to operate its review programs. To meet the minimum requirements for matching general-revenue funds, the agency has been forced to divert resources from other activities that are not subject to user fees or user-fee goals. To sustain user-fee funding, the agency faces growing pressure to meet the performance targets. A failure to either provide matching resources or meet performance standards could result in a catastrophic disruption of all review activities.

The user-fee program has a 5-year term. It will expire in 2012, unless renewed by the current Congress.

Finding 2-8 Congressional appropriations for operation of the 510(k) clearance process have been unstable and frequently inadequate throughout its 35-year life. User fees have increased the level of funding for premarket review activities but not other CDRH operations. The 5-year term of the user-fee program and the risk that it might lapse if various conditions are not met do not ensure stability.

SUMMARY OF FINDINGS

- Finding 2-1 The safety and effectiveness of individual preamendment Class II medical devices has not been systematically reviewed. Continued use in clinical practice, however, provides at least a level of confidence in the safety and effectiveness of preamendment Class II medical devices still on the market.
- Finding 2-2 The 510(k) clearance process was not designed in 1976 to evaluate the safety and effectiveness of new medical devices but only to assess their similarity to preamendment devices.
- Finding 2-3 A 510(k) decision made by the FDA creates a precedent that is legally binding on the agency unless it has rescinded the decision or has barred the device covered by that decision from the market through other legal actions.
- Finding 2-4 The 510(k) clearance process was not designed to reward, recognize, or encourage innovation. At most, promotion of innovation was a byproduct of a process that, by minimizing unnecessary regulatory burdens, facilitated the entry into the market of new devices that did not raise novel questions of safety or effectiveness.
- Finding 2-5 With limited exceptions, a determination by the FDA that one device is “substantially equivalent” to another device does

not reflect an FDA evaluation of the safety or effectiveness of either device.

- Finding 2-6 The 510(k) clearance process has evolved from 1976 to the present through administrative and legislative changes, narrowing the array of issues that the FDA may consider in a 510(k) review and limiting the type of evidence that the FDA could require. Over 35 years, there has been a high frequency of finding substantial equivalence.
- Finding 2-7 The gap in relative burdens on manufacturers between the 510(k) process and the PMA process created by the 1976 law has been maintained by administrative and legislative changes, which have encouraged preferential use of the 510(k) process.
- Finding 2-8 Congressional appropriations for operation of the 510(k) clearance process have been unstable and frequently inadequate throughout its 35-year life. User fees have increased the level of funding for premarket review activities but not other CDRH operations. The 5-year term of the user-fee program and the risk that it might lapse if various conditions are not met do not ensure stability.

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3

Components of US Medical-Device Regulation

From the inception of device regulation under the 1976 Medical Device Amendments, it was understood that devices would be subject to various degrees of premarket review, depending on their risk classification (see Chapter 2). In addition, all devices, once they entered the marketplace (by whatever review mechanism) would be subject to a wide array of regulatory requirements. Premarket review and regulatory control after market entry were intended to operate together to provide a structure that would protect the public's health while not inhibiting innovation.

The committee notes several times throughout this report that the 510(k) process does not operate in isolation. It is part of a larger framework of regulatory tools. This chapter provides an overview of the components of medical-device regulation that come into play after a product is marketed and then an introduction to the available paths for premarket review of devices, including the 510(k) clearance process.

TOOLS AND AUTHORITIES FOR REGULATING MARKETED DEVICES

In general, medical-device regulation is described by following the typical life cycle of a device, starting with research and development, progressing to premarket review by the Food and Drug Administration (FDA), following with regulatory requirements while the device is marketed, continuing with evolution of the device into several (often many) iterations and newer variants, and ending with product obsolescence (IOM, 2010; Kahan, 2009). To focus attention on the incremental aspects of premarket review, however,

this chapter will begin with the FDA's "general controls"—the regulatory system applicable to devices once they enter the marketplace. Once the "postmarket" system is understood, the supplemental controls provided by premarket review can be better appreciated.

In its "Preliminary Report and Recommendations," the FDA Center for Devices and Radiological Health (CDRH) 510(k) Working Group states (FDA, 2010a) that

the aim of the 510(k) program is two-fold: (1) to assure, through a quality review process, that marketed devices, subject to general and applicable special controls, provide a reasonable assurance of safety and effectiveness; and (2) to foster innovation. Robust premarket review is an essential component of CDRH's medical device oversight. *CDRH's postmarket tools, while valuable, have important limitations and are not sufficient to serve as a substitute for high-quality premarket review* [emphasis added].

This chapter explores those potential or perceived limitations and the procedures by which the controls are imposed and enforced.

Controls Affecting Marketed Devices

The statute establishes a combination of prohibitions and mandates with which a device and its manufacturer must comply. Some of the mandates are imposed on specific devices by order of the FDA at its discretion; others are adopted through regulations issued by notice-and-comment rule-making. This discussion covers only the legal authority of the FDA, not how that authority may have been used through individual enforcement actions or the exercise of discretion not to act.

Many of the controls apply to all devices, regardless of risk presented or classification; others apply to a subset of devices based on risk but not classification; and a few apply only to devices classified in Class II or Class III. Compliance with the controls is monitored and enforced by the FDA through its own resources and with the assistance of the US Department of Justice (DOJ) and federal courts.

The following text will review prohibitions and mandates related to all devices, prohibitions and mandates related to higher-risk devices, FDA monitoring systems, FDA enforcement powers, and procedural requirements that may affect the FDA's ability to use the powers granted by law.

Controls Applicable to All Devices

Prohibitions

Contamination

A device may not consist in whole or in part of any filthy, putrid, or decomposed substance¹ or contain an unsafe color additive.²

Container Contamination

The container of a device may not be composed in whole or in part of any poisonous or deleterious substances that may render its contents injurious to health.³

False Claims of Compliance

The marketer of a device may not claim that it complies with a performance standard established by or recognized by the FDA, unless the device conforms in all respects to the standard.⁴

False or Misleading Labeling

The labeling of a device may not be false or misleading in any particular.⁵ It may not fail to make all required disclosures conspicuous and accessible to potential users under customary conditions of sale.⁶ Whether labeling is misleading is determined both by what is said and by what material information is omitted in light of what is said.⁷

Unsafe When Used in Accordance with Instructions

A device may not be dangerous to health when used as suggested in its labeling.⁸

Mandates

Registration of Manufacturers

A US-located manufacturer, processor, packager (or reprocessor and repackager⁹) of a medical device must register with the FDA the business's

¹Federal Food, Drug, and Cosmetic Act [hereinafter FFDCA] § 501(a)(1); 21 USC § 351(a)(1) (2006).

²FFDCA § 501(a)(4), 21 USC § 351(a)(4)(B) (2006).

³FFDCA § 501(a)(3), 21 USC § 351(a)(3) (2006).

⁴FFDCA § 501(e), 21 USC § 351(a)(1) (2006).

⁵FFDCA § 502(a), 21 USC § 352(a) (2006).

⁶FFDCA § 502(c), 21 USC § 352(c) (2006).

⁷FFDCA § 201(n), 21 USC § 321(n) (2006).

⁸FFDCA § 502(j), 21 USC § 352(j) (2006).

⁹Reprocessors and repackagers may sterilize, refurbish, or repackage previously used devices. There are special requirements for those who reprocess single-use medical devices. Section 502(v); 21 USC 352(v) (2006).

name and all places of business.¹⁰ Any additional place of business must be registered immediately.¹¹ Registration is also required for establishments outside the United States where devices are made for importation into the United States.¹² Registration is to be electronic.¹³

Listing of Products

Each registered person must file with the FDA a list identifying each device made or processed for commercial distribution in the United States.¹⁴ The label and labeling¹⁵ for each listed device and a representative sample of other labeling must be provided.¹⁶ The FDA may request a registrant to provide a statement as to why it believes that any product listed is not subject to a performance standard or a premarket approval (PMA) application requirement.¹⁷ If a device previously listed is no longer made, the registrant must provide a notice of discontinuance regarding the product.¹⁸ Listings are to be electronic.¹⁹

Label Information

The label is affixed to the device or its immediate container.²⁰ The label of a device must prominently disclose the company name, trade name, or trade symbol of the original manufacturer.²¹ It must also disclose the name and place of business of the manufacturer, packager, or distributor and the quantity of contents in the package.²² The device must be identified by its established or common nonproprietary name (if any).²³

Labeling with Adequate Instructions for Use

The labeling of a device must provide adequate directions for use and adequate warnings against unsafe use.²⁴ The FDA has historically required

¹⁰FFDCA § 510(c), 21 USC § 360(c) (2006).

¹¹FFDCA § 510(d), 21 USC § 360(d) (2006).

¹²FFDCA § 510(i), 21 USC § 360(i) (2006 & Supp. II 2008).

¹³FFDCA § 510(p), 21 USC § 360(p) (2006).

¹⁴FFDCA § 510(j)(1), 21 USC § 360(j)(1) (2006).

¹⁵A label is written matter affixed to a device or its immediate packaging. Labeling includes labels and other written materials accompanying the device (for example, an operator's manual or detailed product information). The FDA also includes some promotional materials in the scope of labeling. For this chapter, promotional labeling is treated with advertising, below.

¹⁶FFDCA §§ 510(j)(1)(A)–(B), 21 USC § 360(j)(1)(A)–(B) (2006).

¹⁷FFDCA § 510(j)(1)(D), 21 USC §§ 360(j)(1)(D) (2006).

¹⁸FFDCA § 510(j)(2)(B), 21 USC § 360(j)(2)(B) (2006).

¹⁹FFDCA § 510(p), 21 USC § 360(p) (2006).

²⁰FFDCA §§ 201(k)–(l), 21 USC §§ 321(k)–(l) (2006).

²¹FFDCA § 502(u), 21 USC § 352(u) (2006).

²²FFDCA § 502(b), 21 USC § 352(b) (2006).

²³FFDCA §§ 502(e)(2), (4), 21 USC §§ 352(e)(2), (4) (2006).

²⁴FFDCA § 502(f), 21 USC § 352(f) (2006).

that directions be adequate for a layperson, both as to the conditions for which the device is to be used and as to the safe and effective way to use the device.²⁵ The statute permits the FDA to exempt devices from these requirements, which the agency has done by declaring them (or allowing their manufacturers to declare them) to be prescription devices,²⁶ for which the labeling need only be written for healthcare professionals, not laypersons.²⁷ To take advantage of that exemption, however, the labeling must also provide information that permits a healthcare practitioner to use the product safely and for the purpose for which it is intended.²⁸

If a device is intended for use in healthcare facilities or by healthcare professionals, labeling required for a prescription device may be made available solely by electronic means and need not be included physically with the device package.²⁹

Design and Manufacture of Products

Every device must be designed, manufactured, packed, stored, and installed in conformity with current good manufacturing practice regulations established by the FDA.³⁰ The regulations mandate use of design validation, investigation of complaints, a corrective and preventive action plan to identify root causes of product nonconformance with standards and specifications and to implement effective actions to prevent recurrence, and a quality system to oversee and ensure compliance with the FDA requirements and internal company procedures.³¹

Reports of Removals and Corrections

A manufacturer or importer must report to the FDA any device correction (for example, a software upgrade, change in operating instructions, or field modification) or removal (for example, recall, field recovery, or replacement) if the correction or removal was undertaken to reduce a risk to health posed by the device or to remedy a violation of the FFDCA caused by the device that may have presented a risk to health.³² The FDA has promulgated regulations to implement this provision.³³

²⁵21 CFR § 801.5 (2009).

²⁶Prescription devices are not the same as restricted devices, although an individual device may be both. See below regarding restricted devices.

²⁷FFDCA § 502(f), 21 USC § 352(f) (2010); 21 CFR § 801.109 (2009).

²⁸21 CFR § 801.109 (2009).

²⁹FFDCA § 502(f), 21 USC § 352(f) (2006).

³⁰FFDCA §§ 501(h), 520(f)(1), 21 USC §§ 351(h), 360j(f)(1) (2006).

³¹21 CFR pt. 820 (2009).

³²FFDCA § 519(g), 21 USC § 360i(g) (2006).

³³21 CFR pt. 806 (2009).

Reporting of Adverse Medical Events by Manufacturers and Importers

In general, each manufacturer or importer of a medical device legally marketed in the United States must keep records and make reports to the FDA regarding deaths or serious injuries that the device may have caused or to which it may have contributed.³⁴ Malfunctions that did not cause or contribute to deaths or serious injuries must also be reported if a death or serious injury would be likely to result should the malfunction recur.³⁵ The agency has implemented this authority through regulations.³⁶

Reporting of Adverse Medical Events by Device-User Facilities (Not Manufacturers)

Hospitals, ambulatory surgical facilities, nursing homes, and outpatient diagnostic and treatment facilities (other than physician offices) are required to report to the FDA information that reasonably suggests that a device has or may have caused or contributed to the death or serious illness of or serious injury to a patient of the facility.³⁷ There is no comparable user-facility reporting requirement for drugs. This requirement has been implemented through regulations issued by the FDA.³⁸ (Adverse-event reporting is discussed in detail in Chapter 5.)

Controls Applicable Only to Higher-Risk Devices**Restricted Devices**

If the FDA determines that a device's potential for harm or collateral measures necessary for its use are such that there cannot be reasonable assurance of its safety and effectiveness without the restriction, the agency is authorized to require that the device be restricted to sale, distribution, or use, only on the written or oral authorization of a healthcare practitioner or "upon such other conditions as [the FDA] may prescribe."³⁹ The statute goes on to suggest both the types of other conditions that the FDA might consider and limitations of these conditions if used:

No condition . . . may restrict the use of a device to persons with specific training or experience in its use or to persons for use in certain facilities unless [the FDA] determines that such a restriction is required for the safe and effective use of the device. No such condition may exclude a person

³⁴FFDCA § 519(a), 21 USC § 360i(a) (2006). See 21 CFR pt. 803 (2009) (implementing regulations).

³⁵FFDCA § 519(a)(8), 21 USC § 360i(a)(8) (2006).

³⁶21 CFR pt. 803, subpts. D–E (2009).

³⁷FFDCA § 519(b), 21 USC § 360i(b) (2006).

³⁸21 CFR pt. 803, subpt. C (2006).

³⁹FFDCA § 520(e), 21 USC § 360j(e) (2006).

from using a device solely because the person does not have the training or experience to make him eligible for certification by a certifying board recognized by the American Board of Medical Specialties or has not been certified by such a Board.⁴⁰

That authority is exercised at the FDA's discretion and may be imposed in any of three ways: by regulation issued through a notice-and-comment rule-making (usable for devices in any class),⁴¹ as part of a performance standard established by notice-and-comment rule-making (usable only for Class II devices),⁴² or as a condition for the approval of a PMA application (usable only for Class III devices).⁴³

Although the language is quite similar to that used by the FDA to determine whether a device should be a prescription device,⁴⁴ the designations as "restricted device" and "prescription device" are technically distinct. Numerous devices are recognized as "prescription devices" by their manufacturers and the FDA through labeling and fall under exemptions from the "adequate directions for use" requirements.⁴⁵ Those devices, however, are not "restricted devices" unless separately designated by the FDA.

The FDA has generally used the restricted-device authority via the PMA application process and rarely by regulation (Hutt et al., 2007). Only a very few Class II devices are formally "restricted."⁴⁶

As early as 1983, however, the FDA was being criticized in Congress for failing to use its power to impose *other* conditions on use:

The legislative history [of the 1976 amendments] explains that Congress sought to supersede and add to the existing authority used by the FDA to limit sale or use of certain devices except by prescription. Authority beyond prescription was necessary because many . . . believed that major problems arose from misuse of devices by practitioners, and not just from manufacturing or design defects. Establishing conditions under which devices could be used, or limiting or describing the facilities where they could be used, or the training or qualification of those who use them in treatment, was envisioned as a way to address user-related problems. Controls such as these were not contemplated by the lone previously existing authority to limit devices to a practitioner's prescription.⁴⁷

⁴⁰*Id.*

⁴¹*Id.*

⁴²FFDCA § 514(a)(1), (b), 21 USC § 360d(a)(1), (b) (2006).

⁴³FFDCA § 515(d)(1)(B)(ii), 21 USC § 360e(d)(1)(B)(ii) (2006).

⁴⁴21 CFR § 801.109(a) (2009).

⁴⁵See above regarding "Labeling with Adequate Instructions for Use."

⁴⁶21 CFR § 801.420, 21 CFR § 809.30, 21 CFR § 864.4020(d).

⁴⁷Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce, 98th Cong., Medical Device Regulation: The FDA's Neglected Child (Comm. Print 98-F).

Once a device is designated as a restricted device, two additional important legal consequences—apart from limiting access to the device to or through physicians—result:

- *Advertising and Promotional Materials.* The promotion of medical products is generally regulated by the Federal Trade Commission (FTC), with no official role for the FDA with two exceptions. The FDA has jurisdiction to regulate the advertising of prescription drugs. With regard to prescription devices, however, the agency is given jurisdiction only to regulate advertising for prescription devices that are also restricted devices. The marketer is prohibited from advertising a restricted device with materials that are “false or misleading in any particular.”⁴⁸ In addition, all advertisements for a restricted device must provide the device’s established or common name (if any) and a brief statement of the product’s intended uses, side effects, and contraindications.⁴⁹ Because the FDA has declined to restrict almost all Class II devices, responsibility for preventing false or misleading advertising for these devices has remained exclusively with FTC.
- *Inspections.* During inspections of manufacturing plants, the FDA is authorized by one provision of the statute to see the production and distribution records related to restricted devices but not to devices that are not restricted.⁵⁰ A separate provision, however, empowers the FDA to inspect any records that are required by law to be kept.⁵¹ The agency has directed that specific production and distribution records on all devices be kept as part of good manufacturing practice requirements.⁵² Thus, the failure to designate devices as restricted has not adversely affected the FDA’s ability to examine manufacturing records.

Controls Related Only to Class II or Class III

Device Tracking

The FDA may require a manufacturer to adopt a method for tracking a Class II or Class III device whose failure might be reasonably likely to have serious adverse health consequences, that is intended to be implanted for more than 1 year, or that is a life-sustaining or a life-supporting device

⁴⁸FFDCA § 502(q)(1), 21 USC § 352(q)(1) (2006).

⁴⁹FFDCA § 502(r), 21 USC § 352(r) (2006).

⁵⁰FFDCA § 704(a), 21 USC § 374(a) (2006).

⁵¹FFDCA § 301(e), 21 USC § 331(e) (2006).

⁵²FFDCA §§ 501(h), 520(f)(1), 21 USC §§ 351(h), 360j(f)(1); 21 CFR pt. 320, subpt. M.

used outside a device-user facility.⁵³ In 2002, the FDA set forth three new nonbinding criteria in addition to those in the statute to determine whether device tracking might be required: the likelihood of sudden, catastrophic failure; the likelihood of serious adverse clinical outcomes; and the need for prompt professional intervention.⁵⁴

Tracking requires that the manufacturer keep records of the name and address of each patient who received the device, the physician who prescribed the device, and (if different) the physician who is following the patient. The agency has issued regulations creating the general requirements for complying with this provision.⁵⁵ The authority to impose tracking requirements is discretionary with the FDA and is exercised by an “order” to individual manufacturers covering each affected device.⁵⁶

Postmarket Surveillance

The FDA may require a manufacturer to conduct surveillance of a Class II or Class III device that meets any of the criteria for device tracking (above) or is expected to have substantial use in pediatric populations.⁵⁷ “Postmarket surveillance” is a specific activity defined by the statute and is not to be confused with “postmarketing surveillance,” which encompasses a wide array of programs, including adverse-event reporting by manufacturers and user facilities, third-party safety monitoring, and FDA–academic collaborations. Surveillance generally cannot last more than 36 months and must be designed to provide useful data that could reveal unforeseen adverse events or other information necessary to protect public health.⁵⁸ The FDA has issued general regulations governing requirements when surveillance is ordered.⁵⁹ Imposing a requirement for surveillance is discretionary with the FDA⁶⁰ and is done by an “order” to the manufacturer of the affected device or, in the case of pediatric devices, as a condition for clearance of a Class II device or approval of a Class III device.⁶¹

⁵³FFDCA § 519(e), 21 USC § 360i(e) (2006).

⁵⁴Medical Devices; Device Tracking, 67 Fed. Reg. 5,943, 5,944 (Feb. 6, 2002) (codified at 21 CFR pt. 821).

⁵⁵21 CFR pt. 821 (2009).

⁵⁶21 CFR § 821.20 (2009).

⁵⁷FFDCA § 522(a), 21 USC § 360l(a) (2006).

⁵⁸FFDCA § 522(b), 21 USC § 360l(b) (2006).

⁵⁹21 CFR pt. 822 (2009).

⁶⁰FFDCA § 522(a)(1), 21 USC § 360l(a)(1) (2006).

⁶¹FFDCA §§ 522(a)(1)(A)–(B), 21 USC §§ 360l(a)(1)(A)–(B) (2006).

Special Controls

Class II devices may be subject to one or more “special controls” to supplement the general controls to provide reasonable assurance of safety and effectiveness.⁶² The definition of a Class II device specifies that it is

a device which cannot be classified as a Class I device because the *general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness* of the device, and for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines . . . , recommendations, and other appropriate actions as [the FDA] deems necessary to provide such assurance⁶³ [emphasis added].

In parallel, the definition of Class III covers devices that cannot be classified as Class I because general controls are insufficient to ensure safety and effectiveness and that cannot be classified as Class II because “insufficient information exists to determine that the special controls . . . would provide reasonable assurance of its safety and effectiveness.”⁶⁴

The statute does not require, however, that every Class II device be subject to special controls. Although the definitional sentences just quoted state that “general controls . . . are insufficient,” the definition of Class II goes on to provide that

for a device that is purported or represented to be for a use in supporting or sustaining human life, [the FDA] shall examine and identify the special controls, *if any*, that are necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance⁶⁵ [emphasis added].

By implication, for a Class II device that is not so represented, the FDA is not even obliged to consider special controls. In addition, the various types of special controls identified in the statute (discussed below) are all written to be discretionary with the agency. As a practical matter, the FDA has always treated special controls as a discretionary matter. Today, roughly 15% of all device types classified in Class II are subject to special controls (Desjardins, 2010).

The statutorily authorized “special controls” can include one or more of the following:

⁶²FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

⁶³*Id.*

⁶⁴FFDCA § 513(a)(1)(C), 21 USC § 360c(a)(1)(C) (2006).

⁶⁵FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

- Device tracking (patient registries) and postmarket surveillance, as discussed above. Each authority is exercised in individual cases by order of the agency.
- “Performance standards” that are promulgated either by the FDA (through an elaborate notice-and-comment rule-making)⁶⁶ or by a third party and recognized by the FDA (through a simple published notice).⁶⁷ Performance standards may cover the construction, components, ingredients, and properties of a device and its compatibility with power systems and connections with these systems; testing requirements; provisions for measurement of performance; and requirements for submission of test results to demonstrate conformity. A performance standard may also specify that the device is a restricted device in the same manner in which the FDA might restrict the device under separate authority (see above).⁶⁸
- FDA guidelines, including guidelines on the submission of clinical data with a 510(k) notification.⁶⁹ The FDA has adopted a form of notice-and-comment procedure for the adoption of guidelines (which the FDA now calls guidances).⁷⁰
- FDA recommendations. The statute refers only to “recommendations” without specifying what they might address or how a recommendation would become an enforceable control.⁷¹ The agency may, in issuing recommendations, use the same procedures as for guidances.⁷²
- Any “other appropriate actions.” The FDA is authorized to adopt any other special control that it deems necessary to provide a reasonable assurance of safety and effectiveness.⁷³

For a number of reasons, however, special controls have not transformed and cannot transform the 510(k) process into one based on safety and effectiveness rather than one based on substantial equivalence to a predicate device. First, as noted above, only about 15% of all Class II device types are subject to special controls. Second, some premarket special controls are focused on a particular aspect of the device, such as medical devices that include an antimicrobial agent, or on generic procedures for conducting research for a class of devices, such as animal studies for cardiovascular

⁶⁶FFDCA § 514(b), 21 USC § 360d(b) (2006).

⁶⁷FFDCA § 514(c), 21 USC § 360d(c) (2006).

⁶⁸FFDCA § 514(a)(2), 21 USC § 360d(a)(2) (2010).

⁶⁹FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

⁷⁰21 CFR § 10.115 (2009).

⁷¹FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

⁷²21 CFR § 10.90(c) (2009).

⁷³FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

devices (FDA, 2007b, 2010d). These guidances are not intended to supplant the standard for premarket clearance, which remains substantial equivalence to a predicate device, not safety and effectiveness. Third, many special controls are nonmandatory guidance documents, and they bind neither the FDA nor the regulated industry. For example, the guidance document for tissue adhesive with an adjunct wound-closure device intended for the topical approximation of skin explains that it “does not create or confer any rights for or on any person and does not operate to bind FDA or the public” and states that manufacturers are free to “use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations” (FDA, 2010c). Manufacturers using an alternate must, however, show that the binding legal requirements are fulfilled. Fourth, some special controls, such as postmarket surveillance and device tracking, are postmarket forms of regulation that are based on the recognition that the premarket data on safety and effectiveness on some Class II devices may not identify long-term risks or rare events. Finally, practical considerations probably preclude the issuance of special controls for each component of every Class II device. Developing a special control is highly resource-intensive, and in the case of a novel device, the necessary expertise to do so may be lacking (GAO, 1988). Thus, resource constraints presumably would prevent the FDA from taking on such a task. In addition, a proliferation of special controls could become a hurdle to innovation as a further barrier to bringing new devices to market.

The committee believes that special controls can provide a reasonable assurance of safety and effectiveness for some Class II devices. The FDA's use of those controls, however, neither has transformed the 510(k) process into a form of comprehensive safety and effectiveness review nor represents a mechanism for doing so in the future.

Food and Drug Administration Monitoring Powers

Monitoring the Marketplace and Clinical Experience

Much of the FDA's awareness of problems comes from information voluntarily submitted by consumers, physicians, insurers, and competing manufacturers; from reports in the mass media; and from routine surveillance of the marketplace. However, the agency has tools that require parties to submit information to permit it to oversee what products are in clinical use, whether they are being used safely, and whether manufacturers are complying with the requirements of the law.

Information Provided by Manufacturers and Importers

- Who is making what? The requirements for registration and product listing provide the FDA with an inventory of those supplying medical devices to the market and the devices being supplied.
- Product labeling. The FDA reviews only draft labeling, not final labeling, during the 510(k) review process, and marketers may make some types of changes in labeling without seeking additional FDA review. The FDA can obtain by inspection, or in some cases via the Internet, the current labeling of any device. It thus can assess the adequacy of directions for use, warnings, and other critical information for patients or healthcare professionals for that device.
- Product defects. Reports of removals and corrective actions allow the FDA early warning of potential safety issues and an opportunity to evaluate the adequacy of a manufacturer's remedial and preventive actions.
- Product-related adverse events. Reporting both of individual cases and of trends permit the FDA to identify potential safety issues.
- Postmarketing surveillance. Reports from structured surveillance programs (including those mandated by the FDA order to individual manufacturers, those funded by the FDA, and those run through third-party collaborations) may supply a more comprehensive database (with both numerator and denominator data) in which to look for risks posed by medical devices.

Information Provided by Third Parties

- Device-related adverse events at device-user facilities. Mandatory and voluntary reporting of individual cases by end users in health facilities provides the FDA with an alternative source of potential safety information.
- Voluntary reports of adverse events from physicians, patients and third parties. Although not legally obliged to do so, many healthcare practitioners and patients submit MedWatch reports to the FDA regarding medical devices.
- Other voluntary reports and submissions of information. Competitors are a frequent source of potential violations of the FFDCA.

Inspections

The FDA is authorized to enter factories and warehouses in which devices are manufactured, packed, or held for shipment and to inspect a facility and equipment, finished and unfinished goods, and containers and labeling on the premises.⁷⁴ The agency may obtain records related to move-

⁷⁴FFDCA § 704(a), 21 USC § 374(a) (2006).

ment of devices and components in interstate commerce.⁷⁵ And the FDA may inspect and copy records related to adverse medical events associated with devices, device tracking, and corrections and removals of devices.⁷⁶ The statute says that the FDA may also inspect manufacturing records or other documents related to a medical device if the device is a restricted device.⁷⁷ In that case, the FDA may examine all records (other than financial data, sales data, pricing data, personnel data, and research data) bearing on whether the device is in compliance with the FFDCAs.⁷⁸ With respect to devices that are not designated as restricted, the FDA nevertheless has been able to gain inspectional access to some manufacturing records. The agency has used its powers related to good manufacturing practice regulations to require that some manufacturing records be maintained for all devices;⁷⁹ accordingly, the FDA may inspect these records.⁸⁰

FOOD AND DRUG ADMINISTRATION ENFORCEMENT AND OTHER POWERS

When the agency discovers violations of the law or products that pose unacceptable risks to consumers, it has a wide variety of tools available to try to remedy the situation and to sanction the violators. The committee requested information from the FDA about its use of these authorities, and it was able to provide some information on the numbers and types of enforcement actions that it has taken. Given the different mechanisms needed to use these authorities, however, the agency does not have a centralized system for tracking the actions and was not able to provide the committee with some of the specifics about the actions, including whether they were used with products cleared under the 510(k) program or through other premarket-review pathways.

Judicial Enforcement Powers

The statute provides three remedies or sanctions that can be imposed, but only by order of a federal court, when the FDA finds a product or a manufacturer not in compliance with the law. To obtain such orders, the FDA must work through the DOJ Office of Consumer Litigation and the US attorney's offices around the United States. Procedurally, the FDA must

⁷⁵FFDCA § 703, 21 USC § 373 (2006).

⁷⁶FFDCA § 704(e), 21 USC § 374(e) (2006) (referring to FFDCA § 519, 21 USC § 360i (2006)).

⁷⁷FFDCA § 704(e), 21 USC § 374(e) (2006).

⁷⁸FFDCA § 704(a), 21 USC § 374(e) (2006).

⁷⁹FFDCA § 520(f), 21 USC § 360j(e) (2006); 21 CFR pt. 820, subpt. M.

⁸⁰FFDCA § 301(e), 21 USC § 331(e) (2006).

first convince the DOJ attorneys that a case is meritorious and worth bringing from among the array of legal violations presented for action by other agencies. Then, the DOJ attorneys must present the matter before a federal judge (and perhaps a lay jury) and win a judgment or verdict.

To get a judicial action brought, CDRH must first prepare the case and then persuade the FDA associate commissioner for regulatory affairs (and the Office of Enforcement) that the case is meritorious. The associate commissioner is charged with balancing the enforcement initiatives of all components of the FDA, so in a sense CDRH may be competing for a place in line. The proposed action is also reviewed by the FDA Office of Chief Counsel for legal sufficiency. If the associate commissioner for regulatory affairs and chief counsel are favorably moved, the agency refers the matter to DOJ, which conducts an independent review for both legal merit and the likelihood of convincing a judge (or jury) of the merits of government's case. Again, the FDA is competing with other agencies for the attention of DOJ. Thus, the process could appear very cumbersome and time-consuming for CDRH personnel.

The statute sets forth three remedies or sanctions:

- Seizure and forfeiture of violative product. When a medical device is found to be in violation of the prohibitions or mandates applicable to it, the law deems it to be “adulterated” or “misbranded.” The FDA, through DOJ, can obtain a judicial order authorizing a US marshal to seize the product and either secure it on site or remove it to another secure location. Thereafter, a notice is published announcing the action and permitting any interested party (for example, the manufacturer, distributor, retailer, or owner) to file a claim as to the product. If a claim is filed, the case proceeds as a civil action in which the government must prove, by a preponderance of the evidence, that the product is illegally adulterated or misbranded. If the FDA is successful or if no claim is filed, the device is forfeited to the government and can be destroyed. (In some cases, the claimant may seek to bring the product back into compliance under the FDA's supervision.) If the claimant prevails, the device is returned as is.⁸¹ The FDA has advised the committee that in the period FY 2001–2008, it has successfully brought 13 seizure actions (Desjardins, 2011).
- Injunction. The FDA can seek a federal court order restraining persons from violations of the FFDCA. Again, there is an opportunity for the defendant to be tried by a judge, and the government must prove the violation by a preponderance of the evidence.⁸² If the

⁸¹FFDCA § 304, 21 USC § 334 (2006 & Supp. II 2008).

⁸²FFDCA § 302, 21 USC § 332 (2006).

government prevails, the court can, in appropriate cases, also order restitution to the customers of the violator, disgorgement of unjust profits to the government, or both.⁸³ Once an injunction is issued, any further violations can be enforced through a contempt-of-court proceeding. The FDA has informed the committee that in the period FY 2001–2008, it obtained 12 injunctions related to medical devices (Desjardins, 2011).

- Criminal prosecution. The FDA, through DOJ, can prosecute companies and individuals criminally for violations of the law.⁸⁴ Guilt must be proved—usually to a jury—beyond a reasonable doubt. Fines have been substantially increased in recent decades, and prison time for individuals is a possibility although rarely imposed. The FDA reported that its Office of Criminal Investigations successfully obtained 212 criminal convictions for violations of the law in the period FY 2001–2010, which resulted in fines and restitution in excess of \$577 million (Desjardins, 2011).

Administrative Enforcement Powers

Over the years, Congress has supplemented the judicial enforcement tools with others that the agency can use without involving DOJ or a federal court. Some tools “punish” the violator; others deal only with a violative or otherwise unsafe or ineffective product. The FDA is empowered to issue orders—usually after (or concurrent with) administrative proceedings, including formal or informal hearings—to accomplish specific tasks. Most of the authorities apply a criterion related to the risks posed by the device in question; the criteria are quite similar but not identical throughout the authorizing language.

Banning a Device

The FDA may ban a device from sale if it finds that the device “presents substantial deception or an unreasonable and substantial risk of illness or injury.”⁸⁵ If the problem could be corrected or eliminated by labeling changes, the FDA is directed first to provide the manufacturer notice and a reasonable time to modify the labeling before starting a proceeding to ban the device.⁸⁶ To ban a device, the FDA must engage in a notice-and-comment proposal-and-final-order rule-making proceeding to promulgate

⁸³*US v Lane Labs—USA Inc.*, 427 F.3d 219 (3d Cir. 2005); *US v Rx Depot, Inc.*, 438 F.3d 1052 (10th Cir. 2006).

⁸⁴FFDCA § 303(a), 21 USC § 333(a) (2006).

⁸⁵FFDCA § 516(a), 21 USC § 360f(a) (2006).

⁸⁶FFDCA § 516(a)(2), 21 USC § 360f(a)(2) (2006).

a regulation.⁸⁷ The agency may make the rule effective on publication of the proposal if the deception or risk of illness or injury “presents an unreasonable, direct, and substantial danger to the health of individuals.”⁸⁸ Once a device is banned, it becomes an adulterated device subject to the same enforcement powers as any other adulterated device.⁸⁹ According to the FDA, this authority has been used only once since it was established in 1976 (Desjardins, 2011).

Recalling a Device

If the FDA finds that “there is a reasonable probability that a device . . . would cause serious, adverse health consequences or death,” it may order the manufacturer and other appropriate persons (for example, distributors and retailers) to cease distribution of the device immediately and to instruct healthcare professionals and device-user facilities (for example, hospitals and ambulatory surgical centers) to cease use of the device.⁹⁰ After issuance of the order, the FDA must provide an opportunity for an informal hearing, which must consider both the merits of the order and whether the device should be physically recalled; the FDA is to vacate the order if the grounds for the action prove inadequate.⁹¹ After the hearing (if any), the FDA may amend the order to require the physical recall of the device, but no device may be recalled from individuals and a device should not be recalled from a device-user facility if the FDA determines that recalling the device presents a greater health risk than not recalling it.⁹² The FDA was given the power to order recalls in 1990. Nevertheless, most recalls remain voluntary (GAO, 2011). The agency advised that it has not formally tracked recall orders but believes that the authority has been used at least three times in the past 20 years (Desjardins, 2011).

Ordering Risk Notification about a Device

If the FDA finds that a device “presents an unreasonable risk of substantial harm to the public health”, that notification is “necessary to eliminate” this risk, and that “no more practicable means is available” to eliminate the risk, it may order that notification be given by “persons and means best suited under the circumstances involved, to all health professionals who prescribe or use the device and to any other person (including . . . device

⁸⁷FFDCA § 516(a), 21 USC § 360f(a) (2006).

⁸⁸FFDCA § 516(b)(1), 21 USC § 360f(b)(1) (2006).

⁸⁹FFDCA § 501(g), 21 USC § 351(g) (2006).

⁹⁰FFDCA § 518(e)(1), 21 USC § 360h(e)(1) (2006).

⁹¹*Id.*

⁹²FFDCA § 518(e)(2), 21 USC § 360h(e)(2) (2006).

users) who should properly receive notification in order to eliminate such risk.”⁹³ The statute allows the FDA to direct the order to any person (not just a manufacturer or distributor of the device), so healthcare practitioners who have treated patients with the device may be required to notify their patients. Before issuing any notification order, the FDA is to consult with the persons who are to give notice, but no formal or informal hearing is required. The FDA has not tracked the use of this authority (conferred in 1976) but advises that it has not been used many times. It was used once in 2010 (Desjardins, 2011).

Ordering Repair of, Replacement of, or Refund for a Device

If the FDA finds that a device “presents an unreasonable risk of substantial harm to the public health,” that there are reasonable grounds for believing that the device was not properly designed or manufactured with reference to the “state of the art” at the time it was designed or made, that there are grounds for believing that the unreasonable risk was not caused by failure of a person other than the manufacturer or supplier to exercise due care in the installation, maintenance, repair, or use of the device, and that simple risk notification would not by itself be sufficient to eliminate the risk but that repair, replacement, or refund is necessary to do so, it may order the manufacturer to repair the device, to replace it with an equivalent device that does not pose the risk, or to refund the purchase price of the device. The manufacturer is entitled to an opportunity for an informal hearing before the order takes final effect.⁹⁴ The FDA has not used this provision since it was enacted in 1976, because the agency has found it difficult to establish that a device did not conform to the “state of the art” when first manufactured. The FDA did enter into a consent decree of permanent injunction in 2010 that required the defendant to replace or refund the price of a device, but this order was not issued under the statutory provision (Desjardins, 2011).

Imposing Civil Money Penalties

If the FDA finds that any company or individual (or both) has violated any requirement of the FFDCCA related to a medical device, it may impose a civil money penalty in an amount not exceeding \$15,000 for each violation and not exceeding \$1 million for all violations adjudicated in a single proceeding.⁹⁵ Exceptions are made for some technical violations, such as a violation of good manufacturing requirements that involves devices that

⁹³FFDCA § 518(a), 21 USC § 360h(a) (2006).

⁹⁴FFDCA § 518(b), 21 USC § 360h(b) (2006).

⁹⁵FFDCA § 303(f)(1)(A), 21 USC § 333(f)(1)(A) (2006 & Supp. II 2008).

are not defective.⁹⁶ The FDA must provide a formal evidentiary proceeding before the penalty can be enforced.⁹⁷ According to the FDA, civil money penalties have been imposed seven times in the period FY 2001–2008 (Desjardins, 2011).

Detaining a Device in Anticipation of Seizure

If an FDA investigator finds during an inspection of a device that she or he has reason to believe the device violates the FFDCA, the investigator may order the device detained for a reasonable period, not to exceed 20 days. The detention period is to permit the FDA to decide whether to initiate a seizure action or undertake other actions. The manufacturer is entitled to a prompt informal hearing on any detention order.⁹⁸ The FDA does not track the numbers of detention orders that precede seizure. The agency informed the committee, however, that use of this authority is difficult because of the statutory timeframe of 30 days, which is generally not sufficient to process a seizure action (Desjardins, 2011).

Detaining and Denying Entry of Devices Offered for Import into the United States

When an imported device is presented to US Customs and Border Protection (CBP) for release into US commerce, the FDA is to be notified and given an opportunity to inspect the product. The agency may request that CBP detain the device (that is, delay the release) while the FDA determines its compliance with the FFDCA. If the FDA finds that the device fails to comply with a requirement or has violated a prohibition or that the manufacturer did not comply with good manufacturing practice requirements, it can direct CBP to refuse release. The owner or consignee may seek to correct the violation, if that is possible, under FDA supervision. Any device not permitted entry may be destroyed if it cannot be brought into compliance or, in some instances, returned to the country of origin.⁹⁹

In the period 2002–2010, more than 17,500 devices and almost 1,200 diagnostics were refused entry into the United States by the FDA (Desjardins, 2011).

⁹⁶FFDCA § 303(f)(1)(B), 21 USC § 333(f)(1)(B) (2006 & Supp. II 2008).

⁹⁷21 CFR pt. 17 (2009).

⁹⁸FFDCA § 304(g), 21 USC § 334(g) (2006).

⁹⁹FFDCA § 801(a), 21 USC § 381(a) (2006).

Suspending Approval of a Premarket Approval Application

If the FDA finds that continued distribution of a Class III device under an approved PMA application “would cause serious, adverse health consequences or death,” it may temporarily suspend the approval while initiating proceedings to withdraw approval permanently in accordance with formal legal procedures.¹⁰⁰ The manufacturer is entitled to an informal hearing on the suspension order, separate from the formal hearing on the withdrawal. There is no counterpart authority with respect to a 510(k) clearance.

Procedural Requirements

The foregoing has identified a variety of procedures that the FDA is required to use when exercising specific powers. Because CDRH has referred in its preliminary report to “important limitations” of its postmarket controls, it is appropriate to examine what each of the procedures entails.

Notice-and-Comment Rule-Making

The Administrative Procedure Act provides that regulations generally may be issued only after notice of the proposed rule is provided to interested persons and they are given an opportunity to comment before the rule is made final.¹⁰¹ The FDA has adopted detailed procedures for promulgating regulations.¹⁰² This can lead to improvements in the program or the development of an alternative. Given the authority of the FDA or any federal agency, it seems appropriate that stakeholders have the opportunity to comment before requirements are imposed. The process begins with publication of a proposal in the *Federal Register* that sets forth the factual grounds on which the FDA relies for its proposal, the legal authority for the proposed rule, and information on where and how people may submit comments. The FDA will almost always provide at least 60 days after the publication for the public to comment. A final order may be issued any time after the comment period closes. It, too, is published in the *Federal Register* and contains a summary of the comments received, the agency's conclusions, and whatever changes have been made in light of the comments. At least 30 days must elapse before the order may become final, except in some public-health emergencies.

Those simple statutory procedures have been supplemented by two requirements. First, under a presidential executive order, each rule that could affect the economy, increase costs or prices, or substantially and adversely

¹⁰⁰FFDCA § 515(e)(3), 21 USC § 360e(e)(3) (2006).

¹⁰¹5 USC § 553 (2006).

¹⁰²21 CFR § 10.40.

affect competition, productivity, or innovation must be reviewed by the Office of Management and Budget before it is proposed and again before a final order is issued.¹⁰³ Second, the Office of the Secretary of Health and Human Services (the Department of Health and Human Services is the parent organization of the FDA) must review and approve any FDA proposals or final rules that address substantial public issues, such as those affecting the availability, marketability, cost, or quality of regulated products.¹⁰⁴ The process of issuing regulations through notice-and-comment rule-making has thus become more time-consuming and burdensome for the FDA.

The FDA has adopted similar procedures for obtaining public input on guidances or guidelines.¹⁰⁵

Formal Evidentiary Hearing

A formal evidentiary hearing, the counterpart of a civil trial in a courtroom, occurs before an administrative law judge (ALJ) with sworn witnesses, cross-examination, written evidence, and briefs by counsel.¹⁰⁶ Such hearings take considerable time to prepare and conduct and are often preceded by various motions and submissions to frame the issues, determine the admissible evidence, and resolve procedural disputes. After the hearing, the ALJ prepares findings of fact and conclusions and makes an initial decision. Either side may appeal the decision to the commissioner of the FDA, who reviews the record, the initial decision, and the arguments of the parties and issues a final decision. In many situations, a private party who loses a decision after a formal evidentiary hearing may seek review by a federal court.

Informal Hearing

The FDA has established procedures for a “regulatory hearing” to provide an expeditious opportunity for an adversely affected party to be heard on a proposed or actual order.¹⁰⁷ In contrast with a formal hearing, the rules of evidence do not apply. Both sides present their views, a limited amount of cross-questioning may occur, and a written report is issued. But the timeframe for initiating, holding, and completing the process is tightly controlled.

¹⁰³Exec. Order 12,291, 46 Fed. Reg. 13,193 (Feb. 17, 1981).

¹⁰⁴46 Fed. Reg. 26,052 (May 11, 1981).

¹⁰⁵21 CFR § 10.115.

¹⁰⁶21 CFR pt. 12; see also 5 USC § 554 (2006).

¹⁰⁷21 CFR pt. 16.

Order

The FDA may issue an order simply by issuing a written directive to an affected party, provided that the factual predicates for the order are satisfied. The statute may require the agency to provide an opportunity for an informal hearing before or soon after the issuance of an order.

Finding 3-1 The Food and Drug Administration has a wide array of tools to address safety risks that are discovered to be posed by marketed devices.

Finding 3-2 The Food and Drug Administration has not used the tools at its disposal extensively. The Center for Devices and Radiological Health has suggested that there are important limitations in their use. The committee identified some procedural burdens on the exercise of these tools, but these burdens do not in themselves explain the historical and continuing sparse use of the tools.

COMPARISON OF THE FOOD AND DRUG ADMINISTRATION'S AUTHORITIES OVER MARKETED DRUGS AND MARKETED DEVICES

In contrast with the system designed for medical devices, the FDA's drug regulatory framework after the Drug Amendments of 1962 required a more standardized, clinical-trial-based premarket review of both safety and effectiveness of all new drugs and placed less emphasis on postmarket surveillance and management of risks.¹⁰⁸ Until passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA),¹⁰⁹ it could be fairly said that the FDA had better risk-management authorities for marketed devices than it had for approved drugs. The 2007 legislation made important changes in the FDA's powers, which implemented some of the recommendations of the Institute of Medicine report *The Future of Drug Safety* (IOM, 2007). In essence, after 4 decades of extensive, if not often exclusive, reliance on authority to approve new drugs and to remove them later, Congress and the FDA recognized that this model had inherent limitations in ensuring the safety and effectiveness of drug products. The results of premarket clinical trials conducted by trained investigators on relatively small numbers of carefully selected research subjects could not be extrapolated to the use of a drug by thousands of physicians and millions of patients. Unexpected adverse reactions, interactions with other medicines, the

¹⁰⁸Drug Amendments of 1962 (Harris-Kefauver Act), Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 USC).

¹⁰⁹Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 USC).

need for dose adjustments for concomitant diseases, and new uses for other diseases or conditions emerged after approval. Removal of a drug from the market was not always a rational option for addressing the new issues. Thus, although it did not alter the FDA's premarket approval process for drugs, the FDAAA added important new authorities for the FDA to evaluate and manage drug-related risks after approval (Evans, 2009).

Drugs and devices present distinct regulatory issues, and the authorities that the FDA has in connection with drugs may not always be appropriate for devices. Nevertheless, it is instructive to compare the regulatory frameworks as they exist today.

It appears that the FDA already has many authorities over marketed devices that closely resemble the new postmarket authorities that the FDAAA created for drugs. The FDAAA enables the agency to institute a Risk Evaluation and Mitigation Strategy (REMS) plan for an individual drug when necessary to ensure that the benefits of the drug outweigh the risks that it poses. If there is a substantial discrepancy, it lies in the procedural requirements to use the powers granted by Congress. For example, the FDA may be required to promulgate a regulation to exercise an authority for devices, whereas the equivalent authority for drugs can be exercised by means of an order. This procedural complexity may have contributed to CDRH's stated concern about limitations on its statutory authorities, and it tends to increase the effect of FDA's resource constraints.

Authority to Gather Evidence During the Postmarket Period

Table 3-1 compares the FDA's authorities to obtain information regarding risks posed by drugs and medical devices after they enter the marketplace. Here, the term *passive* refers to evidence-gathering that is passive from the *regulator's* perspective—that is, the agency passively awaits data collected and submitted by other parties. *Active* surveillance involves active development of systems to allow the FDA to acquire safety data on its own initiative, for example, through the creation of information systems that allow mining existing administrative or clinical databases.

The FDA is also authorized to engage in the active surveillance of clinical experience for medical products through the Sentinel Initiative (device-specific active surveillance programs are discussed in detail in Chapter 5). In 2007, the FDAAA directed the FDA to develop methods to obtain access to data from disparate sources (including federal health-related data from the Medicare and Department of Veterans Affairs programs and private health-insurance claims) and to construct and validate methods for linking and analyzing safety data from these sources.¹¹⁰

¹¹⁰FDCA § 1005, Pub. L. No. 110-85, 121 Stat 823 (2007).

TABLE 3-1 Comparison of FDA Authorities to Obtain Postmarket Information on Risks Posed by Drugs and Medical Devices

Passive Gathering of Clinical Experience	Approved Drugs	Marketed Devices
Reporting by manufacturers and importer of adverse-event information received by them	Mandatory for all drugs	Mandatory for all devices
Reporting by hospitals and other user facilities of observed adverse events	No authority to require	Mandatory for manufacturer or the FDA
Tracking of users; user registry	Discretionary authority to require as part of REMS	Discretionary authority to require
Reporting by manufacturers and importers of corrections and removals to address risks	No authority to require	Mandatory for all devices
Assessing specific safety issues	Discretionary authority to require as part of REMS or as condition of approval ^a	Discretionary authority to require "postmarket surveillance" study or as condition of Class III approval
Requiring prospective clinical trials	Discretionary authority to require any time that new safety information emerges ^b	Discretionary authority as condition of Class III approval

^aFFDCA § 505(o), 21 USC § 355(o) (Supp. 2007).

^bFFDCA § 505(o), 21 USC § 355(o) (Supp. 2007).

The FDAAA also directed the agency to prepare an analysis of adverse-event reports for each newly approved drug within 18 months after approval or after use by 10,000 people, whichever is later.¹¹¹

Authority to Take Action to Manage Emerging Safety Issues

The FDA has several authorities that allow it to manage safety issues as they occur. These authorities are summarized in Table 3-2.

¹¹¹FFDCA § 505(r)(2)(D), 21 USC § 355(r)(2)(D) (Supp. 2007).

Labeling Changes

The FDA has various authorities to address serious problems of device labeling, but these are procedurally more cumbersome than the process now in effect for drugs. In practice, device labeling changes may require voluntary cooperation of the manufacturer. In contrast, the FDAAA substantially expanded the FDA's authority to require mandatory safety-related labeling changes for already-approved drugs at any point in their life cycle.¹¹² The process calls for the FDA to notify manufacturers of new safety information that the agency believes should be placed in the drug's labeling. There are brief periods for response (30 days) and discussion (30 days), after which the FDA can order the change if agreement has not been reached.

Restrictions on Sale, Distribution, and Use

The FDA has always had authority, after following due-process procedures, to revoke a drug's approval and force it from the market. However, the agency lacked tools for selective risk management that would let a drug remain on the market but require specific measures to manage its risks. The FDAAA provided such authorities. The FDA can condition the sale of a drug on a specific risk-management measure, a REMS.¹¹³ The FDA can require a REMS on initial approval or later if emerging evidence reveal that a REMS is needed to ensure that the drug's benefits outweigh its risks. A REMS must provide for continuing evaluation of risk. Additional elements may be included, such as medication guides, patient package inserts, and warning letters to inform healthcare providers or patients of a risk. The FDA also has authority to impose specific restrictions on the use, distribution, or prescribing of a drug in cases in which a drug is effective but has known risks so serious that the drug otherwise would have to be taken off the market. Those specific restrictions are called elements to ensure safe use and can include such measures as requiring providers to have special training to prescribe the drug, requiring that the drug be used only in specific settings, requiring a registry to monitor patients' outcomes, and requiring patients to be screened before use of the product or requiring them to be monitored for adverse events.

For devices, the FDA has authority to restrict a device of any class if it determines that the restriction is necessary to provide reasonable assurance of safety and effectiveness. The types of use restrictions that can be imposed are in many respects similar to those that can be imposed for drugs under REMS. An important difference is that REMS use restrictions potentially make it possible to limit the use of a drug to patients who have particular

¹¹²FFDCA § 505(o)(4), 21 USC § 355(o)(4) (Supp. 2007).

¹¹³FFDCA §§ 505(p), 505-1, 21 USC §§ 355(p), 355-1 (Supp. 2007).

TABLE 3-2 Comparison of FDA Authorities to Take Remedial Actions in Light of New Safety Findings

FDA Authority	Approved Drugs	Marketed Devices
Banning a product	Discretion to revoke marketing approval; may suspend immediately as an imminent hazard ^a	Discretion to declare product a banned device; discretion (for Class III premarket approval only) to revoke marketing approval
Recalling a product	No authority to compel ^b	Discretion to compel by order
Changing labeling	Discretion to compel labeling change by order ^c	No direct authority to compel by order
Notifying (healthcare practitioners or users) of risk	Discretion to compel by REMS plan ^d	Discretion to compel by order
Restricting distribution or use	Discretion to restrict by REMS plan ^e	Discretion to restrict under restricted-device powers
Compelling special labeling for patients	Discretion to compel by REMS plan or MedGuide program ^f	Discretion to compel through special controls (by notice-and-comment rule-making regarding Class II device) or premarket approval (as condition of approval for Class III)
Ordering repair of, replacement of, or refund for a product	No authority to compel	Discretionary authority to compel by order

characteristics; there is no explicit provision for similarly limiting the use of a device. Another major difference is procedural: the FDA can restrict devices of any class by notice-and-comment rule-making, as part of a performance standard established by notice-and-comment rule-making for Class II devices, or as a condition of approval of a PMA device. Thus, in theory, the FDA has some authorities that would allow dispensers of devices to be subject to restrictions, but the method of imposing restrictions is so procedurally cumbersome as to make it impractical to apply in most circumstances, and there is no explicit provision for adding nuance to the limitations to reflect patient characteristics.

TABLE 3-2 Continued

FDA Authority	Approved Drugs	Marketed Devices
Imposing civil money penalties for violations	No authority (other than for false direct-to-consumer advertising of prescription drugs) ^g	Discretionary authority to impose after formal hearing
Detaining product in anticipation of seizure	No authority to order	Authority to detain upon order
Detaining and denying products offered for import	Discretionary authority identical for drugs and devices	Discretionary authority identical for drugs and devices
Communicating risk–benefit information on marketed products in timely fashion	Required for drug products ^h	No explicit communication program or process, but the FDA has general authority to issue public-health notifications ⁱ

^aFFDCA § 505(e), 21 USC § 355(e) (2006).

^bThe FDA is authorized to undertake multiple seizures of a product. FFDCA § 304(a), 21 USC § 334(a) (2006). Often, the threat of a seizure will induce a recalcitrant company to undertake a voluntary recall.

^cFFDCA § 505(o)(4), 21 USC § 355(o)(4) (Supp. 2007).

^dFFDCA § 505-1(e), 21 USC § 355-1(e) (Supp. 2007).

^eFFDCA § 505-1(f)(3), 21 USC § 355-1(f)(3) (Supp. 2007).

^fFFDCA § 505-1(e)(2), 21 USC § 355-1(e)(2) (Supp. 2007); see also 21 CFR pt. 208.

^gFFDCA § 303(g), 21 USC § 333(g) (Supp. 2007).

^hFFDCA § 505(r), 21 USC § 355(r) (Supp. 2007).

ⁱFFDCA § 705(b), 21 USC § 375(b) (2006).

Timely Communication of Postmarket Risk–Benefit Information

The FDAAA did not alter the FDA's traditional drug-labeling requirements. The statute, however, recognizes that labeling may not be an ideal medium for communicating timely, specific information about emerging drug-safety problems. The FDAAA established an Internet-based system for disseminating risk information to patients and providers (FDA, 2010e).¹¹⁴ The FDA met its statutory deadline to have a basic system in place 1 year after the enactment of the FDAAA.¹¹⁵ The system's functionality continues to develop. The FDAAA envisions that this system will provide a searchable,¹¹⁶

¹¹⁴FDAAA § 915, 21 USC § 355(r) (Supp. 2007).

¹¹⁵*Id.*, 21 USC § 355(r)(1).

¹¹⁶*Id.*, 21 USC § 355(r)(2)(A).

centralized source of information on drug-related risks and how to manage them. The system already incorporates information that traditionally has been provided in paper form, such as labeling, package inserts, medication guides,¹¹⁷ and safety alerts.¹¹⁸ In addition, the system is intended to provide continuous, close-to-real-time feedback of emerging postmarket data, such as early signals of potential safety problems that are not clear enough to support labeling changes.¹¹⁹ The Internet system also will provide risk-management information, including REMS information.¹²⁰

There appears to be no statutory impediment that would prevent the FDA from developing a similar communication system for device labeling and other safety information. Rather, it appears to be a question of resources and priorities.

DEVICE CLASSIFICATION AND PREMARKET REVIEW

As noted earlier, all devices must comply with FDA standards of safety and performance. The 1976 Medical Devices Amendments (MDA) adopted a three-tier system to determine the need for *additional* regulatory controls, in the form of premarket review, to protect and promote public health. The tiers correspond to the perceived risks posed by the devices. In that sense, the law represented a sharp break with the approach taken with respect to pharmaceutical agents, for which a uniform and rigorous system was established for all new agents and an only slightly less demanding and uniform system for generic copies of the agents. Because of the wide variety of devices, Congress recognized that uniformity was neither necessary nor ideal to attain the ultimate public-health goal of a “reasonable assurance of the safety and effectiveness” of each marketed device. A detailed description of device classification criteria is included in Chapter 2.

Using the standards outlined in Chapter 2, the FDA was tasked with reviewing the universe of devices on the market when the 1976 law was enacted—and therefore called preamendment devices—and placing them into the appropriate Class. In addition, the 1976 MDA directed that any device that was not on the market at the time the bill became law (so-called postamendment devices) would be automatically placed in Class III, at least until reclassified.¹²¹

It took the FDA until 1988 to complete the classification of preamendment devices (Hutt et al., 2007).

¹¹⁷*Id.*, 21 USC §§ 355(r)(2)(B)(i)–(ii), 355(r)(3).

¹¹⁸*Id.*, 21 USC § 355(r)(2)(B)(iv).

¹¹⁹*Id.*

¹²⁰FDAAA § 915, 21 USC § 355(r)(2)(B)(v).

¹²¹FDCA § 513(f)(1), 21 USC § 360c(f)(1) (2006).

Premarket Approval Application¹²²

For Class III devices, Congress required affirmative FDA approval before marketing.¹²³ The application for PMA must contain the following major elements: full reports of all information known to or reasonably known to the applicant regarding investigations to assess the safety and effectiveness of the device; a full statement of the components and properties of the device and of the principles of its operation; a full description of the methods used in and facilities and controls used for its manufacture, processing, and (when relevant) packaging and installation; specimens of the labeling proposed to be used for the device; and any other information relevant to the PMA application that the FDA (with the concurrence of an advisory panel) may require.¹²⁴ The statute does not give the FDA authority to waive any of those requirements, but the FDA permits an applicant to omit information that is not applicable to the device if the omission can be justified.¹²⁵

In 2002 and again in 2007, Congress enacted 5-year user-fee programs under which persons submitting PMA applications and 510(k) submissions must pay a fee to underwrite some of the cost of FDA review. Thus, a new PMA application must be accompanied by payment of a fee for FDA review; in FY 2011, the standard fee for a new PMA application was \$236,298, although small businesses can have the fee reduced to \$59,075 (FDA, 2011d).

The agency has 180 days to review a PMA application and either to grant or to deny its approval.¹²⁶ Moreover, the FDA, if requested, must meet with the applicant not later than 100 days after the PMA application is filed and discuss the status of the review, identifying any deficiencies and describing the information needed to correct them.¹²⁷ During the review process of a novel device, the FDA may on its own initiative (and must on request by an applicant) refer the PMA application to an outside advisory panel, which must report its conclusions and recommendations.¹²⁸

Grounds for denial are the lack of demonstration of a reasonable assurance of either safety or effectiveness, noncompliance with good manufacturing practices, and false or misleading labeling.¹²⁹ If the agency denies

¹²²This discussion is highly abbreviated from Appendix A. Its purpose is to provide an overview of the principal premarket-review alternative to the 510(k) submission.

¹²³FFDCA §§ 513(a)(1)(C), 515(a), 515(a), 21 USC §§ 360c(a)(1)(C), 360e(a) (2006).

¹²⁴FFDCA § 515(c), 21 USC § 360e(c) (2006); see 21 CFR § 814.20 for FDA's regulations detailing the required format and contents of a PMA.

¹²⁵21 CFR § 814.20(d).

¹²⁶FFDCA § 515(d)(1), 21 USC § 360e(d)(1) (2006).

¹²⁷FFDCA § 515(d)(3), 21 USC § 360e(d)(3) (2006).

¹²⁸21 CFR § 814.44(a), (b).

¹²⁹FFDCA § 515(d)(2), 21 USC § 360e(d)(2) (2006).

a PMA application, the applicant may request a second review by and a hearing before a hearing officer or a standing outside FDA advisory panel.¹³⁰

The FDA may condition approval on compliance with one or more of a variety of postapproval requirements, including the completion of studies to confirm the safety, effectiveness, and reliability of the device for its intended use.¹³¹

Once a PMA application is approved, the applicant must obtain additional FDA approvals before making changes in the labeling of the device, its indications for use, its packaging or sterilization procedures, its performance or design specifications, or its components, principles of operation, or physical layout.¹³² In addition, the applicant may not make any changes in the manufacturing procedures without submitting to the FDA a notice describing the change and summarizing the supporting data, which the agency has 30 days to review; if the FDA finds the notice inadequate, the applicant may not implement the modification.¹³³ Finally, after approval of the PMA application, the applicant must make periodic reports to the FDA containing new unpublished reports, if any, of clinical or nonclinical investigations involving the device or related devices and reports from the scientific literature concerning the device.¹³⁴ Revisions of devices approved through the PMA application process require a supplemental PMA application as opposed to a 510(k) submission. Thus, the obligations of the PMA application process extend well past the initial review and approval.

User fees for PMA supplements in FY 2011 range from \$3,800 to \$236,000, depending on the type of supplement and hence the FDA resources needed to review it. There are substantial reductions for small businesses (FDA, 2011d).

510(k) Clearance-Process Submission

The 1976 law contemplated that the sponsor of a new product that was classified in Class I would submit a notice to the FDA at least 90 days before marketing; the notice would set forth the simple fact that the device was so classified. That notice became known as a 510(k) notification after the section of the MDA that required a manufacturer to notify the FDA of a new product before marketing it.¹³⁵ If the agency concurred (or failed to respond within 90 days), the product could enter the market; if not, the

¹³⁰FFDCA § 515(g), 21 USC § 360e(g) (2006).

¹³¹21 CFR § 814.82.

¹³²FFDCA § 515(d)(6), 21 USC § 360e(d)(6) (2006); limited exceptions are provided in 21 CFR § 820.39(d).

¹³³FFDCA § 515(d)(6), 21 USC § 360e(d)(6) (2006).

¹³⁴21 CFR § 814.44.

¹³⁵FFDCA § 510(k), 21 USC § 360(k) (2006).

sponsor was notified that the product could not enter the market without further action, such as approval of a PMA application. In 1990, Congress modified the law to prohibit the launch of a new product until the FDA had issued a written response to the 510(k) submission.¹³⁶ In 1997, Congress again amended the 1976 law and eliminated the requirement of a 510(k) submission for most Class I devices.¹³⁷

For premarket review of a Class II device, the 1976 law seemed to contemplate that the sponsor of a new product would submit to the FDA a notice under Section 510(k) setting forth the fact that the device was classified in Class II and, if a performance standard had been promulgated, that appropriate certification or evidence that the product conformed to the standard.¹³⁸ As with Class I, the original law did not require FDA action on the 510(k) submission; but in 1990, Congress amended the law to require a written FDA response to the submission before marketing. At the same time, the broader concept of “special controls” was substituted for (but still included) the narrower “performance standard” in the definition of Class II. In 1997, Congress exempted a small proportion of Class II device types from 510(k) submission requirements.

There is no standardized format for a 510(k) submission, although the FDA has issued guidance for manufacturers (see Chapter 4) (FDA, 2005). The 510(k) submission needs to set forth a device’s proposed intended use, the device to which substantial equivalence is claimed, and evidence demonstrating the equivalence. That information may be based on bench testing, animal studies, or clinical trials. Although a 510(k) submission is usually far leaner than a PMA application, the number of pages in the average 510(k) submission has grown over the years and in some cases might be as high as in a regular PMA (FDA, 2010a).

The same legislation that established user fees for PMA applications required fees for the review of 510(k) submissions. In FY 2011, the standard fee is \$4,348, discounted to \$2,174 for small businesses (FDA, 2011d).

The most important development after 1976 was the evolution of the 510(k) clearance process from a transitional tool for preclearance of postamendment devices to a permanent and dominant means of premarket review for most postamendment devices.

¹³⁶FFDCA § 513(i)(1)(A), 21 USC § 360c(i)(1)(A) (2006) (added by SMDA § 12, 104 Stat. at 4523).

¹³⁷FFDCA § 510(l), 21 USC § 360(l) (2006) (added by FDAMA, § 206(a), 111 Stat. 2338-39 (1997)).

¹³⁸FFDCA § 510(k), 21 USC § 360(k); § 514(a)(1)(B), 21 USC § 360d(a)(1)(B) 2006).

Comparison of 510(k) and Premarket Approval Application Requirements

From the perspective of a device manufacturer, the 510(k) clearance process currently offers (and historically has offered) a number of advantages over the PMA application pathway. Table 3-3 summarizes some of the key differences.

Because the 510(k) submission does not include much of the information required in a PMA application, the time needed for preparation of the

TABLE 3-3 Summary of Key Differences Between PMA Applications and 510(k) Submissions

	Premarket Approval Application	510(k) Submission
Detailed description of device components	Required	Not required
Detailed description of methods of manufacture	Required	Not required
Specimens of draft labeling	Required, reviewed, and approved	Required and reviewed, but not approved
Studies regarding safety and effectiveness	Reports of all studies relevant to safety and effectiveness required; clinical trials commonly required	Only studies demonstrating substantial equivalence to predicate needed; clinical trials infrequently needed
Filing fees (FY 2011) (regular business; small business)	\$236,298; \$59,075	\$4,348; \$2,174
Statutory time for FDA review	180 days	90 days
Conditions on final FDA action	Postapproval conditions authorized	Postclearance conditions not authorized
Need for FDA action on changes in manufacturing, labeling?	Generally, FDA approval required; thus, changes are subject to user fees	Generally, FDA clearance not required for manufacturing and labeling changes; thus, these changes are not subject to user fees; other changes—in design, materials, and intended uses—do require a new 510(k) submission
Subject to FDA revocation or rescission?	Yes	Generally, no

submission is usually less, and the scope of issues that can emerge during FDA review is narrower. The committee was advised by industry that it prefers the flexibility and economy of the 510(k) process (IOM, 2010). It is important to note, however, that the 510(k) process was never intended to be a substitute for the PMA process.

Finding 3-3 The 510(k) clearance pathway is generally more economical, faster, and less burdensome to industry and the Food and Drug Administration than the premarket approval application route and has substantially fewer postmarketing controls.

From a public-health standpoint, the differences between the two pathways are less clear. For example, some patient advocates advised the committee that they wanted premarket clinical trials of safety and effectiveness for more devices, but other experts questioned the feasibility of such trials in light of the time required to plan, execute, and analyze the studies; the small numbers of subjects that might be eligible for trials in any given period (limiting the power of studies to detect differences between the new product and alternate treatments); and the pace of technologic change (IOM, 2010, 2011). Determining the “value added” to device safety and effectiveness by requiring a PMA application, as opposed to a 510(k) submission, would be complex and difficult and was not part of the committee’s charge.

INFRASTRUCTURE OF THE CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

As noted in Chapter 2, the FDA and CDRH have faced resource and capability limitations and competing priorities over the life of the medical-device regulatory programs. The limitations have shaped the organization’s approach to fulfilling its mission and created shortcomings in the programs that are difficult to address. Given the increasing number and complexity of devices and combination products that include devices, CDRH’s mission would be difficult even under ideal circumstances. This section explores the resource constraints and strategic issues that affect CDRH and its work.

Financial Resources

The total budget (including mandatory and discretionary spending) of the Department of Health and Human Services in FY 2008 was \$722 billion (see Figure 3-1). Of the \$1.2 billion used to support the FDA’s medical-products programs, \$275 million supported the medical-devices program, compared with \$681 million for the drug program and \$234 million for the biologics program. All the FDA’s programs are considered discretion-

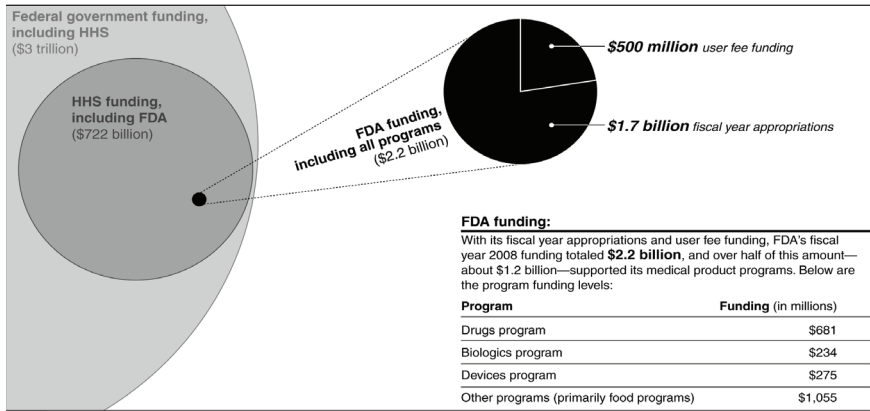


FIGURE 3-1 Federal government, Department of Health and Human Services, and FDA funding, FY 2008.

SOURCE: GAO, 2009a.

ary spending (GAO, 2009b). CDRH’s funding is augmented by user fees. However, as described in Chapter 2, there are limitations to how those funds can be used.

The funding for CDRH has grown from \$159 million in 1999 to \$275.3 million in 2008—a 73% increase (GAO, 2009a). Despite the increase in funding, agency officials reported that the limitations placed on the use of the user-fee funds seriously undermine their ability to meet their responsibilities in programs not supported by user fees (GAO, 2002, 2009a). About two-thirds of all the funding for medical-products program centers (both user-fee funding and discretionary funding) supports user-fee-related activities (for example, submission review). Funding for the program centers increased three times as fast as funding for the FDA’s field operations, which are responsible for inspecting manufacturing facilities (GAO, 2009b).

Staffing

The FDA is concerned about its ability to attract and retain key staff who have essential expertise, such as biologists, chemists, computer programmers, and epidemiologists (GAO, 2009b). For all the FDA centers—CDRH, the Center for Biologics Evaluation and Research (CBER), and the Center for Drug Evaluation and Research (CDER)—full-time equivalents (FTEs) funded by user fees increased by 113% from 1999 (856 FTEs) to 2008 (1,825 FTEs), whereas FTEs funded through appropriations declined

by 7% from 1999 (4,069 FTEs) to 2008 (3,802 FTEs).¹³⁹ In an effort to reduce staffing levels in programs funded through appropriations, the agency offered buyouts to some employees in FY 2004–2006 (GAO, 2009b). CDRH and the Office of Regulatory Affairs (ORA) estimated that they increased their use of contractors to fulfill their responsibilities during that period but were unable to provide the Government Accountability Office (GAO) documentation of total number of contractor hours. The decrease in FTEs resulted in a backlog in work (GAO, 2009b).

CDRH staff are required to respond within 90 days of receipt of a 510(k) notification. In 2009, the FDA's goal was to review 90% of 510(k) submissions within 90 days and 98% within 150 days (GAO, 2009b).¹⁴⁰ Given the variability in the 510(k) submissions, FDA staff report that review times did not allow sufficient review of complex issues (FDA, 2011a). Over a 7-year period, the number of FTEs dedicated to processing 510(k) submissions has risen dramatically, from 166 in 2003 to 249 in 2009. The number of FTEs dedicated to processing PMA applications has grown from 133 to 152 in the same period (Desjardins, 2011). The FDA reported that it takes about 2 years to train new staff to review applications (GAO, 2009b). This long training period makes average annual turnover of 11–13% in the centers (CDER, CBER, and CDRH) an important issue for the FDA (GAO, 2009b).

In 1989, GAO recommended that the FDA collect basic management information, such as staffing (including contractors), to estimate its future needs better (GAO, 1989). The FDA disagreed with that recommendation, indicating that the resources needed to collect the information would detract from the agency's oversight responsibilities. In a 2009 report, GAO reiterated its recommendation with the assertion that the collection of this information is essential for the agency to be able to fulfill its mission adequately. Without the information, it is also impossible for external groups to verify whether the FDA is fulfilling its oversight requirements and optimizing its performance (GAO, 2009b).

Third-Party Review

In August 1996, the FDA initiated a voluntary third-party review pilot program for selected devices. The pilot's purpose was to provide manufacturers of eligible devices an alternative review process that might yield more rapid marketing clearances and enable the FDA to use its scientific review resources for higher-risk devices. All Class I and 30 select Class II device types were eligible for third-party review. The eligible Class II devices were

¹³⁹These numbers do not include contractors.

¹⁴⁰Compared with PMA reviews, for which the goals are 60% of original PMA submissions within 180 days and 90% within 295 days (GAO-09190).

subject to a device-specific guidance or a recognized consensus standard. Well-recognized road maps for establishing device performance were considered important in choosing products to be reviewed in the pilot because such documents would, it was believed, standardize the review process among third-party organizations. The FDA developed an accreditation and training process to ensure that third-party reviewers had the capacity to perform credible reviews and to avoid conflict of interest.

The 1997 FDAMA formally recognized and extended the program. The FDAMA directed the FDA to accredit third parties to review devices of low to moderate risk and to set limits on the number of Class II devices that would be ineligible for third-party review. In September 1998, the FDA published an expanded list of Class II device types eligible for third-party review for which there were no device-specific guidances or standards. For a third party to review a device not subject to a guidance or standard, it must (FDA, 2009)

- Have completed three successful 510(k) reviews in the program.
- Agree to contact the appropriate CDRH branch chief or designee to discuss issues and review criteria.
- Prepare a summary of the discussion and submit it to the Office of Device Evaluation with its 510(k) review.

The third party charges a fee to submitters for review. Once a review has been completed, it must be submitted with a cover letter, a letter from the submitter authorizing submission, a summary of the presubmission discussion described above, the complete 510(k) submission, and a completed review. In addition, there must be a certification that the reported information accurately reflects the data reviewed. The FDA supervisory official is expected to review the third-party submission and make a decision on the submission within 30 days of receipt.

GAO found that often the third-party review could be faster than FDA review for traditional 510(k) submissions but that, as FDA review has become more efficient, the number of third-party reviews is likely to decrease (GAO, 2009c).

As of February 2011, 670 Class I and Class II device types were eligible for third-party review. No Class II devices that are intended to be permanently implanted, that are intended to be life-sustaining or life-supporting, or whose 510(k) submission requires clinical data are eligible for third-party review (GAO, 2009c). Since 2004, about 250 510(k) submissions have participated in the third-party process per year (see Figure 3-2).

Quality assessments were completed on 75% of third-party reviews received during the last 9 months of FY 2005. Overall, major problems were observed by supervisors who reviewed submissions in 31% of reviews;

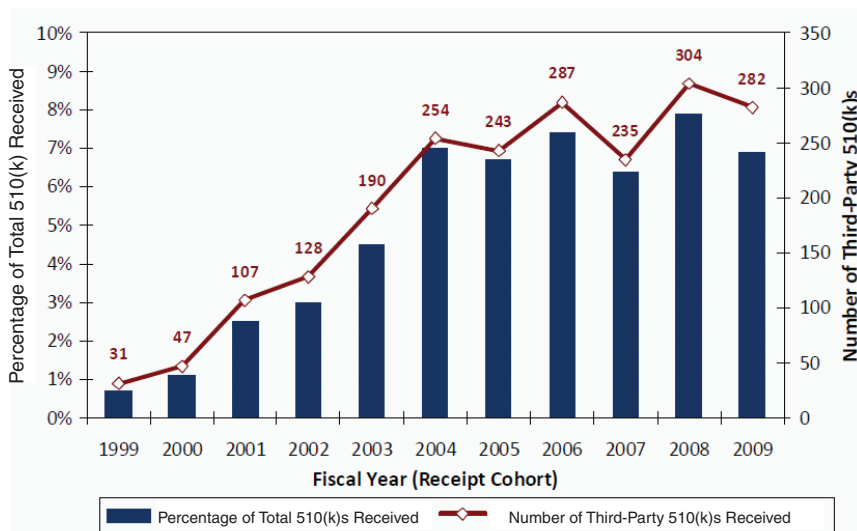


FIGURE 3-2 Third-party 510(k) submissions as percentage of total 510(k) submissions received, FY 1999–2009.

SOURCE: FDA, 2010a.

the most common problems were lack of rationale for conclusions and recommendations, failure to provide an adequate comparison with a legally marketed device, and failure to resolve deficiencies in the 510(k) submission or to address FDA requests (see Table 3-4) (von Eschenbach, 2007). A review of recall data from 2003–2009 found that 510(k) devices cleared via third-party review were more common among recalled devices than among nonrecalled devices (9.9% vs 7.3%) (IOM, 2011). Given the rate of review deficiencies and the higher recall rate, it is not certain that the program has met its goal of assisting the FDA in reducing its work burden.

Information-Sharing and Technology

Inadequacies in information-sharing and technology in the FDA are felt at all levels and centers in the agency. In 2007, the FDA produced a strategic action plan that focused on four strategic goals: strengthening the FDA, improving the safety of patients and consumers, increasing access to new medical and food products, and improving the safety and quality of manufactured products and the supply chain (FDA, 2007a). Improvement of the medical-product review process to increase the predictability and transparency of decisions was identified as a priority. The initiatives included in the plan were the integration of premarket-decision information into a

TABLE 3-4 Frequency of Problems with Third-Party Reviews of 510(k) Submissions

Review Element	% Rated as Minor Issue	% Rated as Major Issue
Presubmission consultation with the FDA	15	4
Rationale for conclusions and recommendations	11	6
Comparison with legally marketed devices—identification and analysis of key similarities and differences	11	5
Summary of device characteristics, intended use, performance, and reason for 510(k)	10	4
Organization and format of review documentation	13	1
Use of guidance and standards	10	2
Scope of reviewer expertise	8	3
Resolution of 510(k) deficiencies and FDA requests	3	5
Determination of device eligibility for third-party review	3	4
Determination of 510(k) administrative completeness	6	1

NOTE: Data based on quality assessments completed by FDA supervisors when making final determinations on 510(k)s with third-party review. The FDA initiated the quality assessments in January 2005.

SOURCE: Adapted from von Eschenbach, 2007.

single comprehensive tracking warehouse accessible to all staff and the pilot testing and evaluation of a Web-based tracking system for premarket review of medical devices (GAO, 2009d).

In a 2009 report, GAO found that although the FDA has an information-technology (IT) modernization project underway, it has failed to develop a comprehensive IT strategic plan to inform the modernization process. A plan would include a well-defined set of goals, strategies, milestones, and performance measures and would allow the agency to consider the human, infrastructure, and funding resources needed. Without a clear plan, GAO asserts, the FDA lacks a roadmap needed to develop an effective system (GAO, 2009d). In addition, CDRH has acknowledged that it is difficult for staff to share knowledge throughout the center (FDA, 2011a). The inability to communicate with other staff, seek essential expertise, and share relevant information can be attributed to problems of individual workload, the lack

of a system to institutionalize cross-center communication, the rigidity of review-turnaround expectations, and the presence of multiple information systems (FDA, 2010b).

In an effort to address its information-systems issues, the FDA has implemented a number of pilot programs that have met with various degrees of success. A program called eConsults is intended to facilitate the exchange of scientific information and staff expertise throughout CDRH. The program, in place for 5 years, fosters communication within CDRH by managing expert-consultation requests and allowing staff to access information and analysis as needed (Desjardins, 2011). It prompts discussion among CDRH offices to access different types of expertise in premarket device submissions, postapproval studies, and compliance and enforcement actions (FDA, 2011b).

CDRH included several items related to the improvement of IT systems in its 2010 strategic priorities. For example, the iReview program, a pilot application begun in 2008, automated the premarket certification of medical devices. The iReview system is a workflow-management tool intended to automate the end-to-end 510(k) review process and to ensure that work is not duplicated in multiple systems, that technical risk is reduced, that future changes in the 510(k) process can be incorporated easily without affecting other applications, and that reviewers, supervisors, and consultants can use one system as a single repository for all 510(k) review status and work products (FDA, 2011c). However, during user-acceptance testing in May 2010, reviewers determined that iReview did not meet the center's most pressing needs, namely, internal searches, reporting, and electronic document routing. As a result, iReview implementation was canceled, and CDRH will work to improve existing tracking systems to perform key functions (Desjardins, 2011).

Another pilot that proved unsuitable was the Appian business-management program introduced in the 2010 strategic priorities. In November 2010, the FDA announced that it would sign a 5-year contract to use this platform in all its centers. The program was intended to improve and align processes between groups and departments and to improve management of several core business processes. Because most of CDRH's core functions involve knowledge creation, the business-management program did not survive the evaluation process and was determined to be the wrong tool for CDRH's work (Desjardins, 2011).

One successful pilot program is the @work toolset, internally known as Traction. Traction is a collaborative tool that combines the attributes of a wiki and a blog with networking capability to forge connections between people throughout the organization. Traction was piloted by CDRH and is now used throughout the FDA (Desjardins, 2011).

Finding 3-4 The Center for Devices and Radiological Health faces persistent challenges because of a lack of or limitations on human, fiscal, and technologic resources and capabilities.

Quality Assurance

The preliminary report of the CDRH 510(k) Working Group finds that “CDRH does not currently have an adequate mechanism to regularly assess the quality, consistency, and effectiveness of the 510(k) program” (FDA, 2010a). That finding is amply supported by the results of the reviewer survey in Appendix D to the preliminary report. The survey asked CDRH personnel who review 510(k) submissions and their managers about their understanding of and opinions on a variety of issues related to making 510(k) substantial-equivalence decisions. In a number of cases, reviewers selected the correct answer only 50–60% of the time, and managers did not do much better (FDA, 2010a).

Problems surrounding quality assurance in the 510(k) process are not new. The first public guidance to aid reviewers and industry in the 510(k) decision-making process was not issued until the program had been operating for a decade (FDA, 1986).¹⁴¹ In 1988, GAO found a lack of a clear officewide policy and a lack of coordination among review divisions, and it recommended steps to improve consistency in 510(k) decision-making and documentation (GAO, 1988). The Department of Health and Human Services inspector general (IG) in 1990 determined that CDRH lacked a comprehensive quality-control program to evaluate and critique the adequacy of the 510(k) review process independently.¹⁴² Three years later, the inspector general issued a follow-up report that concluded that CDRH had focused its quality efforts primarily on the administrative aspects of the 510(k) process, not on the scientific validity of the review decisions.¹⁴³

CDRH has long required device manufacturers to operate a quality system.¹⁴⁴ In an oversimplified description, the regulations prescribe a continuous-improvement process in which specifications and operating procedures are established, persons who have appropriate backgrounds

¹⁴¹Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 336-47 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

¹⁴²Memorandum Re: Internal Control Weaknesses in the Food and Drug Administration's Medical Device 510(k) Review Process, from the HHS inspector general to the HHS assistant secretary for health (July 5, 1990), 2.

¹⁴³Memorandum from the principal deputy inspector general to the acting assistant secretary for health, Re: Follow-Up Review on Internal Control Weaknesses in the Food and Drug Administration's Medical Device 510(k) Review Process (Feb. 26, 1993), 19.

¹⁴⁴21 CFR pt. 820.

are trained in the procedures, execution of the procedures is properly documented, and the resulting output is monitored for conformity to the specifications. When a deviation occurs, the manufacturer is to undertake a root-cause analysis and then implement a corrective-action and preventive-action plan to address the root problem and prevent its recurrence (for example, by revising operating procedures, retraining employees, or revising specifications). The continuous-improvement process is overseen by a quality manager or group and executive management of the company. Those basic principles are as applicable to the making of 510(k) clearance decisions—and any other regulatory decisions (such as PMA application approvals and the use of postmarketing tools to address emerging safety concerns)—as to the production of medical devices.

The absence of a quality system for the 510(k) process since its inception has important consequences for the future of the process. Prior 510(k) clearance decisions are by law binding on the FDA unless a predicate product is removed from the market by the FDA or declared adulterated or misbranded by a federal court.¹⁴⁵ The agency is concerned that its authority to rescind prior decisions may be subject to challenge (Shuren, 2011).

About 120,000 510(k) submissions have been cleared over the past 35 years (Tillman, 2010). As described in Chapter 2, those actions have by and large built on a chain of devices that link a new postamendment device to earlier postamendment devices that ultimately could be traced back to a preamendment device from 1976. CDRH has never had an effective quality-assurance system in the 510(k) process. In addition, at least in the early years of implementation, the FDA may have biased the review process in favor of finding substantial equivalence to avoid the administrative consequences of placing too many devices in Class III (OTA, 1984). Today, CDRH cannot reconstruct the “piggy-backing” of devices without a manual review of perhaps thousands of files. Even if a computerized database allowed easy access to the history, the agency would have to review every decision manually to identify questionable ones. The cost of the exercise would be staggering; the benefit would be, it is hoped, small in terms of identifying devices that should not have gotten to the market by a 510(k) clearance. However, it cannot be assumed that the number is zero.

Finding 3-5 The committee agrees with the CDRH 510(k) Working Group that the Center for Devices and Radiological Health does not have “an adequate mechanism to regularly assess the quality, consistency, and effectiveness of the 510(k) program.”

¹⁴⁵FFDCA § 513(i)(2), 21 USC § 360c(i)(2) (2006).

SUMMARY OF FINDINGS

- Finding 3-1 The Food and Drug Administration has a wide array of tools to address safety risks that are discovered to be posed by marketed devices.
- Finding 3-2 The Food and Drug Administration has not used the tools at its disposal extensively. The Center for Devices and Radiological Health has suggested that there are important limitations in their use. The committee identified some procedural burdens on the exercise of these tools, but these burdens do not in themselves explain the historical and continuing sparse use of the tools.
- Finding 3-3 The 510(k) clearance pathway is generally more economical, faster, and less burdensome to industry and the Food and Drug Administration than the premarket approval application route and has substantially fewer postmarketing controls.
- Finding 3-4 The Center for Devices and Radiological Health faces persistent challenges because of a lack of or limitations on human, fiscal, and technologic resources and capabilities.
- Finding 3-5 The committee agrees with the CDRH 510(k) Working Group that the Center for Devices and Radiological Health does not have “an adequate mechanism to regularly assess the quality, consistency, and effectiveness of the 510(k) program.”

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4

The 510(k) Clearance Process

Chapters 2 and 3 outlined the history of medical-device regulation in the United States and the components of the Food and Drug Administration (FDA) medical-device regulatory infrastructure, including the 510(k) clearance process. This chapter discusses the 510(k) process in more detail. It explains how the FDA has implemented its regulatory authorities¹ and discusses the challenges faced by the FDA and others affected by the program.

The 510(k) submission is the most common premarket regulatory submission received by the Center for Devices and Radiological Health (CDRH) within the FDA. It applies to device types that are generally considered to pose moderate risk and that are not exempt from premarket review but not to high-risk device types that are subject to premarket approval (PMA). The Government Accountability Office (GAO) estimated that in 2003–2007, 31% (15,472) of all devices entered the market through the 510(k) pathway, 1% through PMA, and 1% through programs such as the humanitarian device exemption. The remaining 67% of device types were exempt from premarket review (Class I devices made up 95% and Class II devices 5% of these) (GAO, 2009c).² A study of 510(k) submissions from 1996 to 2009 found that more than 80% of 510(k)-cleared devices were classified as Class II, about 10% Class I, and less than 2% Class III devices (IOM,

¹In this report, the phrase *regulatory authority* refers to the power that the legislature gives the FDA to enforce statutes.

²Data are for the 50,189 devices listed with the FDA by device manufacturers during the period October 1, 2002, through September 30, 2007 (GAO, 2009c).

2011). About 90% of 510(k) submissions for Class I and Class II devices are cleared by the FDA to enter the market (GAO, 2009c).

A number of situations require a manufacturer to submit a 510(k) submission. By regulation, a new 510(k) notification must be submitted if

the device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification: (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process; (ii) A major change or modification in the intended use of the device³ [see Figure 4-1].

Although they are not specified in the 510(k) regulation, there are generally four categories of parties who must submit a 510(k) submission to the FDA (FDA, 2010f):

1. Domestic manufacturers introducing a device into the US market.
2. Specification developers introducing a device into the US market.
3. Repackagers or relabelers who have made labeling changes or whose operations substantially affect the device.
4. Foreign manufacturers or exporters or US representatives of foreign manufacturers or exporters introducing a device into the US market.

The 510(k) clearance mechanism rests on the notion of “substantial equivalence.” A device must be found to be substantially equivalent to a predicate device if it is to be cleared through the 510(k) process for commercial distribution. To be considered substantially equivalent, devices must meet criteria that are detailed in Figure 4-1.

Congress has mandated that the FDA give priority review to PMA applications that have innovative or breakthrough technology.⁴ There is no legal framework for the FDA to request or consider whether a 510(k)-eligible device is innovative with the review process.

IMPLEMENTATION OF THE 510(K) PROCESS

The Medical Device Amendments of 1976 provided that all post-amendment devices were automatically to be classified into Class III—that is, as high risk—with specific exceptions.⁵ The primary exception involved

³21 CFR § 807.81 (a)(3).

⁴FDCA § 515(d)(5); 21 USC § 360e(d)(5) (2006).

⁵FDCA § 513(f)(1), 21 USC § 360c(f)(1) (2006).

a postamendment device that was “substantially equivalent” to a “type of device” that either was a preamendment device that had not been classified or was not a preamendment device but had already been classified into Class I or Class II.⁶ Another exception provided that a postamendment device would not be in Class III if the FDA, in response to a petition, classified it into Class I or Class II.⁷ The ultimate intention was that even postamendment devices would be classified, on the basis of risk, into the appropriate category. Until then, any new product proposed for marketing after 1976 would be subject to PMA requirements unless it were substantially equivalent to a preamendment device already in Class I or Class II (or not yet classified) or reclassified by the FDA down from Class III. This structure would place enormous resource demands on the agency as technology evolved and newer devices were developed. The agency would either have to process increasing numbers of PMAs or have to go through a reclassification process that was procedurally cumbersome, labor-intensive, and time-consuming.

Instead, the FDA permitted the manufacturer of a postamendment device to demonstrate “substantial equivalence” to a preamendment device in Class I or II as part of the 510(k) submission.

Substantial Equivalence

As detailed in Appendix A, the FDA adopted a broad reading of the term *substantial equivalence* and used the 510(k) pathway to avoid requiring PMAs for (or down-classifying) many new and novel devices that would have been placed in Class III (Hutt et al., 2007, *supra* note 11, 986).^{8,9,10,11,12} Congress had not defined substantial equivalence in the 1976 law. The FDA’s liberal interpretation permitted the agency to clear

⁶FFDCA § 513(f)(1)(A), 21 USC § 360c(f)(1)(A) (2006).

⁷FFDCA § 513(f)(1)(B), 21 USC § 360c(f)(1)(B) (2006).

⁸Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env’t of the H. Comm. on Energy and Commerce*, 100th Cong. 345 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env’t).

⁹*Food and Drug Administration Oversight: Hearing Before the Subcomm. on Health and the Env’t of the H. Comm. on Energy and Commerce*, 102d Cong., pt. 2, at 1 (1992).

¹⁰Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env’t of the H. Comm. on Energy and Commerce*, 100th Cong. 337 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env’t).

¹¹*Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env’t of the H. Comm. on Energy and Commerce*, 100th Cong., 384 (1987) (statement of James S. Benson, Deputy Director, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services).

¹²Guidance on the CDRH Premarket Notification Review Program (K86-3) (June 30, 1986) available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm>.

most postamendment devices as substantially equivalent to preamendment devices or even to a postamendment device previously cleared through the 510(k) process (a process known as piggybacking one device onto a series of precedents). By 1989, the agency was concerned that an adverse court ruling on this approach would cripple the 510(k) clearance process and force many new devices into the PMA system. The FDA sought¹³ and in 1990 obtained congressional ratification of its interpretation when the following language was added to the statute:

A. For purposes of determinations of substantial equivalence . . . the term “substantially equivalent” or “substantial equivalence” means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that [the FDA] by order has found that the device –

(i) has the same technological characteristics as the predicate device, or

(ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including clinical data if deemed necessary by [the FDA], that demonstrates that the device is as safe and effective as a legally marketed device and (II) does not raise different questions of safety and efficacy than the predicate device.

B. For purposes of subparagraph (A), the term “different technological characteristics” means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.¹⁴

Congress did not define *predicate device* but prohibited the use as a predicate of any device removed from the market by the FDA or found by a court to have been adulterated or misbranded.¹⁵ As mentioned in Chapter 3, the FDA has not used these authorities widely.

The change provided legal support for the FDA's policy of piggybacking various 510(k) submissions in a string of decisions, so a new product could rely on any lawfully marketed device as a predicate and substantial equivalence to a preamendment device did not have to be established. Also, by being permitted to show that its product was “as safe and effective as” a predicate (instead of merely having substantially equivalent safety and effectiveness), a 510(k) submitter could improve the safety and effectiveness of its device without triggering the risk of being found not substantially

¹³*Medical Device Safety: Hearings Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 101st Cong. 172 (1989–1990) (statement of James S. Benson, Acting Commissioner, Food and Drug Administration).

¹⁴FFDCA § 513(i)(1), 21 USC § 360c(i)(1) (added by SMDA § 12, 104 Stat. at 4523).

¹⁵FFDCA § 513(i)(2), 21 USC § 360c(i)(2) (added by SMDA § 12, 104 Stat. at 4523).

equivalent and having to undergo a PMA review. Thus, a new device might be *superior* to its predicate and still be substantially equivalent to it. “In this way, the standard for safety and effectiveness in a determination of substantial equivalence will evolve slowly as the prevailing level on the market changes, rather than being tied solely to comparison with a pre-1976 device.”¹⁶ In contrast, the change did not require reliance on the best predicate device, so a product that was truly inferior to the current state of the art could still enter the market if the manufacturer could identify any predicate that had not been removed from the market and to which it was substantially equivalent. Once a device is cleared through the 510(k) process and becomes eligible as a predicate, it cannot be removed from the pool of available predicates unless it has been banned or declared adulterated or misbranded and pulled from the market. The FDA estimates that 29% of the devices that have been cleared either were never marketed or were marketed but are no longer available (FDA, 2010b). Whether that reflects deficiencies in product safety or effectiveness, cost, utility, or competitiveness is not known. Nevertheless, the discontinued (or never launched) products may all serve as predicates for future devices. The FDA is unable to dictate which predicates can be selected for 510(k) decision-making. In some cases, the FDA has published guidance documents advising manufacturers on how to demonstrate the predicate relationship. These guidance documents are nonbinding on the manufacturer or the agency.

Devices are constantly updated with minor changes throughout their life cycle for a variety of reasons. The FDA has issued guidance on device modifications and on when a new 510(k) submission is required (FDA, 1997).¹⁷ This guidance does not require manufacturers to report all minor changes or series of minor changes to the agency. The decision of when there has been a significant enough change or series of changes to trigger a new 510(k) submission is largely at the discretion of the manufacturer. Incremental design changes are difficult to define and if poorly controlled can lead to device “creep,” in which there is the potential for a marketed device to differ significantly from a device cleared through the 510(k) review.

Predicates

Identifying an appropriate predicate is a central component of the 510(k) process. The FDA maintains databases that are used to identify predicate devices from a catalog of previously cleared devices. Classifications can be found by searching the Product Code Classification Database. Products are cataloged by using both classification symbols and product-

¹⁶H.R. REP. NO. 101-808, at 25.

¹⁷Updated guidance was issued by the FDA on July 27, 2011, after the committee had completed its work.

code symbols, known as procodes. Procodes are unique three-letter product identifiers assigned by the FDA to all products (whether classified or not). The databases can be searched by product name, manufacturer, whether the device is a preamendment or postamendment device, or procode (FDA, 2009c).

The critical process of identifying predicates is hampered by problems with data systems and information-sharing within CDRH. The Product Code Classification Database is subject to nuances in spelling, formatting, and errors in entries and is unwieldy and difficult to use.¹⁸ In addition, the application of procodes by the FDA has been inconsistent, and there is no user-friendly glossary of this information. Those technical issues often make it difficult to track cleared products (FDA, 2010c).

More detailed information on predicate devices can be obtained through a 510(k) summary or a 510(k) statement. A 510(k) summary or 510(k) statement is required for all 510(k) submissions (FDA, 2010e). The 510(k) summary must provide sufficient detail to understand the basis for a determination of substantial equivalence (FDA, 2010e). In lieu of a 510(k) summary, the manufacturer can opt for a 510(k) statement. The 510(k) statement is a certification that the manufacturer will provide information supporting the FDA finding of substantial equivalence to any person within 30 days of a written request (FDA, 2010e). The Office of In Vitro Diagnostics posts a decision summary on line for devices that it clears through the 510(k) program. The Office of Device Evaluation (ODE) does not post decision summaries on line (FDA, 2010h).

The FDA has acknowledged that information provided to manufacturers for the purpose of identifying predicates is often limited, that 510(k) summaries often lack critical details that might be of value to companies, and that the procode process used in the databases is not transparent (FDA, 2010b). Medical-device manufacturers, in general, agreed with that assessment and suggested that the agency eliminate the 510(k) statement and require a standardized summary and a better method of categorizing products to allow identification of predicate devices (FDA, 2010d).¹⁹ The FDA has proposed posting on line a verified 510(k) summary, photographs and schematics of the device to the extent that they do not contain proprietary information, and information showing how cleared 510(k) devices are re-

¹⁸For example, Letter from the Medical Imaging and Technology Alliance to FDA, Docket Number FDA-2010-N-0054-0055 (March 19, 2010); Letter from AdvaMed to FDA Docket Number FDA-2010-N-0054-0058.1 (March 19, 2010); Comments from James W. Lewis, Salus Ventures, LLC to FDA, Docket Number FDA-2010-N-0054-0015.1 (March 8, 2010).

¹⁹For example, Presentation by R. Glenn Neuman, New World Regulatory Solutions, Docket Number FDA-2010-N-0054-0010.1 (February 18, 2010); Comments by Charmaine Sutton, The Tamarack Group, Docket Number FDA-2010-N-0054-0014.1 (March 6, 2010); Comments by Beth Johnson, Medline Industries Inc., Docket Number FDA-2010-N-0054-0016.1 (no date given).

lated to each other and identifying the premarket submission that provided the original data on or validation of a particular product type. This proposal has raised concerns in industry about the protection of proprietary information (FDA, 2010b, 2010c, 2011a).

Once an appropriate predicate has been identified, the objective of the 510(k) submission is to demonstrate that the new device under review is substantially equivalent to the predicate(s). If it is determined that the device under review has different technologic characteristics from the predicate(s), the FDA may request additional information to evaluate whether the new device is as safe and as effective as the predicate. As mentioned in Chapter 2, about 15% of Class II and Class III 510(k) submissions in FY 2005–2007 had new technologic characteristics (GAO, 2009b).

The FDA, in an internal review of its 510(k) program, noted the difficulty of making comparisons when new issues of safety and effectiveness have been identified; industry representatives, in public comments, noted a lack of predictability in whether the agency would consider a design or material change important enough to constitute a technologic change that would affect the substantial-equivalence justification. The FDA and industry both noted a lack of consistency in the core evidence being requested by the agency for equivalence decisions; industry suggested that this was a process problem (FDA, 2010b, 2010d).

Over the history of the program, systems for tracking and linking 510(k) decisions and predicates have been insufficient (see Chapter 3). As a result, it would be difficult for anyone to trace back the chain of predicates leading to the preamendment device in connection with a device currently on the market. Given that circumstance, the committee finds it important to note that a fundamental difference exists between the 510(k) and PMA pathways. In reviewing a PMA, the FDA must ask, Is this device reasonably safe and effective for its intended use? The 510(k) review asks, Is this device substantially equivalent to some other device whose safety and effectiveness may never have been assessed?

Finding 4-1 The 510(k) process determines only the substantial equivalence of a new device to a previously cleared device, not the new device's safety and effectiveness or whether it is innovative. Substantial equivalence, in the case of a new device with technologic changes, means that the new device is as safe and effective as its predicate.

Finding 4-2 Current 510(k) decisions have been built on a chain of predicates dating back to devices on the market in 1976. Because data systems in the FDA are inadequate, the agency does not have the ability to trace the supporting decisions.

Pushing the Limits of Predicates

As technology moves forward and more sophisticated devices are developed, the threshold of how predicates can be used in the 510(k) review is expanded and broadened. For the most part, manufacturers prefer to use the 510(k) process rather than the PMA process even for more complex devices because of the burden presented by the PMA process. The incentives for manufacturers to seek entry into the market through the 510(k) process rather than the PMA process are discussed in Chapter 3.

The FDA has cited the practice of multiple and “split” predicates as important challenges in the 510(k) review process (FDA, 2010b). 510(k) submissions that use split predicates combine two or more predicates: one or more predicates for claiming intended use and one or more for claiming technologic characteristics. Split predicates have been used for a variety of devices, including devices with incremental changes. 510(k) submissions that use multiple predicates combine functions of more than one predicate device. The FDA’s concern about multiple and split predicates in device submissions stems from an internal analysis that showed a greater mean rate of adverse-event reports related to devices whose 510(k) submissions cited more than five predicates (FDA, 2010b).

CDRH’s internal working group recommended further analysis of multiple predicates and issuance of clarifying guidance on the use of multiple and split predicates in an effort to improve transparency and reproducibility of the review process. The center has not proposed stopping the use of multiple predicates (FDA, 2011a). CDRH proposed elimination of or restriction in the use of split predicates. However, industry groups voiced concerns that eliminating or limiting the use of split predicates may have a chilling effect on innovation (FDA, 2011a).²⁰

Key Regulatory Terms

The determinations of “intended use” and “indications for use” are critical elements in the 510(k) process because they directly affect the determination of substantial equivalence (see Figure 4-1). To continue through the 510(k) process, a new device must have the same intended use as its predicate. However, a device is not required to have the same indications for use as the predicate (FDA, 2010b). A 510(k) submission may include new or different indications for use as long as they do not affect the safety and effectiveness of the device by having different intended therapeutic, diagnostic, prosthetic, or surgical uses from the predicate. It is important

²⁰In January 2011, CDRH announced that it no longer intends to use the term *split predicate*. It plans to issue guidance to clarify the circumstances under which it is appropriate to use multiple predicates to demonstrate substantial equivalence (FDA, 2011a).

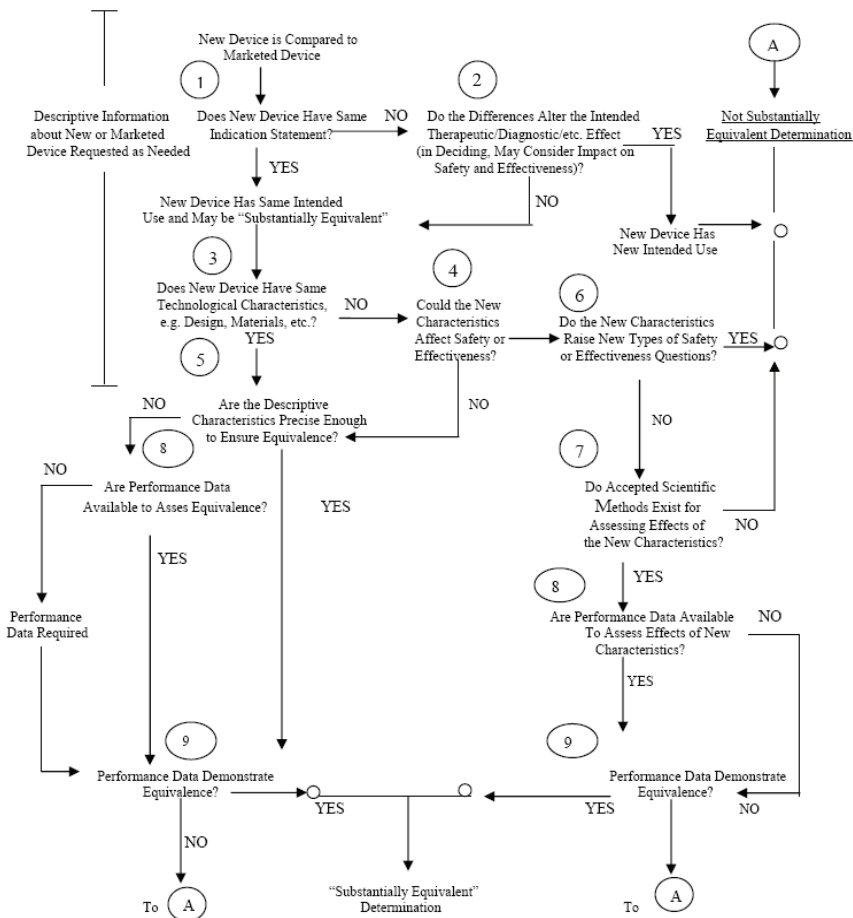


FIGURE 4-1 The FDA substantial-equivalence decision tree. SOURCE: FDA, 2009a.

to note that terms *intended use* and *indications for use* were developed for other regulatory purposes but have been adapted by CDRH to be used as part of the substantial-equivalence decision-making process of the 510(k) review (FDA, 1997).

As stated above, intended use is one of the legal standards that the FDA is required to adhere to in making a determination about substantial equivalence. The definition of a device in the statute twice uses the standard of something that is “intended for use” in disease or in affecting body struc-

ture or function.²¹ The safety and effectiveness of a device are judged with respect to persons for whose use the device is intended and with respect to the conditions of use suggested in the labeling.²²

The FDA's regulations state that the intended uses of a device are "objectively" determined based on the persons legally responsible for the labeling of the device by written or verbal statements of those persons (for example, in product labels and labeling, marketing materials, or in reports to investors) or the circumstances surrounding the distribution of the device.²³ The uses that a seller intends for its product thus govern whether the agency has jurisdiction over the product and whether the product is a device, drug, or biologic.

The phrase *indication for use* is not found in the statute. It is adapted from the regulations for the PMA process,²⁴ which are in turn patterned on the prescription-drug approval process.²⁵ The phrase is a key part of the essential directions to a healthcare practitioner on using the product safely and effectively. For prescription-drug approvals, the FDA created a standard format for labeling, which includes an "indications for use" section that describes the purpose of the drug in relation to a disease or condition (such as to diagnose, prevent, or treat for a named disease or a manifestation of the disease).²⁶ The full prescribing information in the labeling must also contain sufficient details to provide for the safe and effective use of the drug, including such information as dosage forms, dose ranges, routes of administration, duration of use, contraindications, and precautions. In the FDA's view, approved labeling content was "authoritative," not "definitive." For medical devices, "indications for use" provides a description of the patient population and disease or condition that the device will diagnose, treat for, prevent, cure, or mitigate.²⁷ The indications for use are meant to represent a relatively precise description of the clinical applications of the device. Indications for use may be derived from clinical studies, may originate from the history of the predicate-device use, or may be defined by the manufacturer.

A difference between intended use and indications for use from a regulatory perspective is that indications for use are contained in the product labeling provided by the seller, whereas intended use may also be found in other marketing materials and activities of the seller. A 510(k) submission does not have to contain the full final labeling. However, the submission does include proposed labels, labeling, and advertisements, which should

²¹FFDCA § 201(h) (2), (3).

²²FFDCA § 513(a) (2) (A), (B).

²³21 CFR § 801.4.

²⁴21 CFR § 814.20(b)(3)(i).

²⁵21 CFR § 201.57.

²⁶21 CFR § 201.5 7(c)(2).

²⁷21 CFR § 814.20(b)(3)(i).

be in sufficient detail to describe the device, its intended use, and the directions for its use.²⁸ 510(k) submissions have only to include a statement of the submitter's intended use of the device.

The distinction between intended use and indications for use is further complicated by the difficulty of clearly differentiating a medical device's general "tool" use and its therapeutic or clinical applications (FDA, 2010b). Devices may span the spectrum of tool and clinical applications:

- A device that has a well-established general intended use as a tool but does not have specific clinical indications for use, such as medical imaging platforms and general surgical devices (for example, suture material, clamps, and retractors).
- A device that has well-established general intended use as a tool and has been expanded to include one or more specific clinical indications for use (such as a surgical laser that evolves to be used specifically for the removal of tattoos or an ablation device that has a general tool use of destruction of soft tissue and has evolved to be used for treatment for specific types of cancer).
- A device that would not be considered a general tool and has only a specific clinical intended use and indication for use, such as a joint replacement.

Determining the intended use and indications for use of medical devices at either end of the foregoing spectrum is relatively straightforward. Problems can arise, however, with devices that fall in the center of the spectrum, that is, general tools that are evolving into devices that have explicit and specific uses that are no longer consistent with use as a general tool.

Device types that are general tools can often be used for multiple clinical purposes, in multiple clinical disorders, and in multiple anatomic locations. In the 510(k) process, it is possible that those types of devices could be required to provide evidence to support the clinical utility of every possible indication, disease state, and anatomic location for the device even if the intended use has not changed. For many devices, that could be an onerous and unreasonable burden.

Some devices, however, evolve so that new versions can be used only for specific clinical indications, such as an ablation device that evolves to be used only for tattoo removal. Given the structure of the 510(k) process (see Figure 4-1), these devices, which are used only for specific clinical indications, may still be able to cite a predicate with a general tool intended use. Manufacturers may not, however, promote an indication for use that is not cleared by the FDA through a 510(k) submission or approved as part

²⁸21 CFR § 807.87(e).

of a PMA. Thus, there is a tension between a manufacturer's desire to get through the 510(k) process as easily and quickly as possible and its commercial desire to advertise the device for particular indications.

GAO noted that about 1% of 5,063 Class II and III submissions reviewed by the FDA in 2005–2007 had a new intended use (GAO, 2009b). Slightly more than 12%, however, had a different indication for use from the predicate, of which more than 99% were found not to have affected the intended use. Of the 510(k) submissions that were found to be substantially equivalent, almost all had the same intended use, whereas more than half the submissions found not to be substantially equivalent had a new intended use (GAO, 2009b). In light of the increasing complexity and diversity of devices that fall within the 510(k) process, it is important to consider the clarity of the key terms in these initial steps that are pivotal in the 510(k) decision-making process. For instance, early recognition of a potential change in intended use can permit CDRH to determine the need for, and thus obtain, appropriate types of expertise and experience for the review; belated recognition may prevent summoning of the necessary human resources.

CDRH's *Preliminary Internal Evaluations—Volume 1: 510(k) Working Group Preliminary Report and Recommendations* found that fluid and ill-defined regulatory terms create confusion and inconsistency in the center and for industry (FDA, 2010b). In particular, CDRH cited concerns about use of such terms as *intended use* and *indications for use*. Given the subjective judgment needed to determine the criteria for evaluating whether a different indication for use may constitute a new intended use, CDRH has stated that it is difficult to ensure consistent decision-making (FDA, 2010b). The difficulty in addressing the influence of indications for use on a device's intended use is exacerbated by the variation in how *intended use* and *indications for use* are used in different guidance documents; in some cases, these terms are used synonymously (FDA, 2010b). Industry has also pointed to the varying interpretations of *intended use* and *indications for use* as an important source of unpredictability in the 510(k) process (FDA, 2010d). As a result, CDRH has proposed the consolidation of the two terms into a single term, *intended use* (FDA, 2010b).

Finding 4-3 The key regulatory terms *intended use* and *indications for use* are poorly defined and are susceptible to varying interpretations that lead to inconsistency in decision-making and create confusion among FDA staff, industry, Congress, the courts, and consumers.

Finding 4-4 The 510(k) clearance process does not consistently recognize distinctions among devices cleared solely as tools, those cleared for specific clinical applications, and general tools that also have specific clinical applications.

Off-Label Use and Its Effect on the 510(k) Clearance Process

The practice of off-label use is encountered with all types of medical products, and the problems that it presents are not peculiar to medical devices or to 510(k)-cleared medical devices. The committee did not consider it within the scope of this study to undertake a detailed analysis of the practice of off-label use, but it did review how the off-label use of medical devices affects the 510(k) process. The term *off-label use* is not found in the statute, nor has the FDA ever issued a definitive interpretation of it. The committee defined, for its discussion, *off-label use* of a 510(k)-cleared medical device to be any use of the device that is not included in the cleared indications for use (if any) or in its statement of intended use.

It is generally argued that off-label uses of medical products may offer clinical benefits as well as potential risks. A physician's perspective on off-label use is focused on concerns different from the FDA's and may include issues of improving patient care, professional ethics, the development of research, malpractice, and insurance reimbursement. Rarely does FDA regulation impinge a physician's freedom to use a device as he or she deems appropriate in the scope of medical practice.²⁹ The scope of the FDA's power to regulate medical practice, traditionally a matter of state regulation, has been a sensitive issue dating back to the legislative debate about passage of the Federal Food, Drug, and Cosmetic Act in 1938.³⁰ Then and when passing the 1962 Drug Amendments, Congress disclaimed an intent of the FDA's regulation of medical products to entail broad regulation of medical practice.^{31,32} However, courts have never found constitutional limits on the FDA's power to regulate physicians,³³ and most legal scholars agree that "there is little doubt under modern law that Congress has ample power to regulate the manufacture, distribution, and use of drugs and medical devices."³⁴ The 1976 Medical Device Amendments expressly authorized the FDA to approve medical devices subject to restrictions on their use and

²⁹21 USC § 396

³⁰See Joel E. Hoffman, *Administrative Procedures of the Food and Drug Administration*, in 2 *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* 12, 17-24 (David G. Adams et al. eds., 1999) [hereinafter *Fundamentals of Law and Regulation*].

³¹S. REP. NO. 87-1744 (1962), reprinted in 1962 USCC.A.N. 2884, 2820-21.

³²Legal Status of Approved Labeling of Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503 (Aug. 15, 1972) (discussing, in the preamble to a proposed rulemaking, Congress's legislative intent in passing the FFDCA).

³³David G. Adams, *The Food and Drug Administration's Regulation of Health Care Professionals*, in 2 *Fundamentals of Law and Regulation*, supra note 29, at 424-25.

³⁴Richard A. Epstein, *Why the FDA Must Preempt Tort Litigation: A Critique of Chevron Deference and a Response to Richard Nagareda*, 1 J. TORT L. art. 5, at 7 (2006), <http://www.bepress.com/jtl/vol1/iss1/art5Epstein>.

distribution,³⁵ showing congressional recognition that the safety of a device may depend as much on how it is used in a clinic setting as on the process through which it is cleared or approved. The Risk Evaluation and Mitigation Strategy provisions of the 2007 Food and Drug Administration Amendments Act reflect a similar view for drugs. Still, as a policy matter, the FDA has generally sought to avoid potential involvement in regulation of medical practice. As discussed in Chapter 3, the FDA has not made substantial use of its statutory authorities to restrict use and distribution of medical devices.

Device makers and sellers, in contrast, are subject to FDA regulation of the marketing, labeling, and promotion of medical devices. Devices may be promoted and advertised only for the uses that the FDA has approved or cleared. The agency does allow the dissemination of scientific information on unapproved or uncleared uses of medical devices in some circumstances as an educational, not promotional, activity. Examples of dissemination activities that are allowed include continuing medical education programs and research published in peer-reviewed scientific and medical journals (FDA, 1998). The potential for off-label use—perhaps facilitated by promotional activities of the manufacturer, perhaps driven solely by medical practice—creates a specific problem for the 510(k) process. This problem is related to the FDA's determination of the intended use and indications for use of a submission. Intended use in a 510(k) submission is reviewed solely on the basis of the proposed labeling. The FDA has the authority to add warnings to the device label for some off-label uses within the 510(k) review, but the agency cannot refuse to clear a device.³⁶ The agency is thus limited in the extent to which it can prevent unsafe or ineffective clinical applications of a proposed device even when these applications are foreseeable and reasonably predictable.

Some devices have multiple potential indications for use. The magnitude of risk associated with some indications for use may be consistent with clearance through the 510(k) process. Others, however, present a greater risk that is more consistent with the requirements of the PMA process. Because of the considerable differences in the burden between 510(k) clearance and the PMA process, including the submission user-fee, data-collection requirements, and time, there is a potential for manufacturers to circumvent PMA of a device for the higher-risk indications and instead seek a 510(k) clearance in connection with the lower-risk indications. CDRH has indicated that the practice of omitting higher-risk indications from the proposed labeling of 510(k) submissions to avoid a more intensive PMA review is an area of concern. CDRH cited examples in which there has been reasonable

³⁵Medical Device Amendments of 1976, Pub. L. No. 94-295, § 2, 90 Stat. 539, 565 (adding Section 520(e) of the Food, Drug, and Cosmetic Act) (codified as amended at 21 USC § 360j(e) (2006)).

³⁶FFDCA § 513(i)(1)(E).

BOX 4-1**Case Study: Biliary Stents in Peripheral Vasculature**

There are small stents whose size makes them suitable for application both in bile ducts and in peripheral vasculature. Because the former indication involves using a product in patients who have advanced cancer and short life expectancies, the long-term durability of the product is not critical with a biliary stent, and the FDA allows biliary stents to be cleared via the 510(k) process. The same stent, if used in peripheral vasculature, would require PMA because long-term risks posed by the device are of greater concern in this patient population. As a result of having multiple premarket-review pathways—510(k) and PMA—available for a single device, it was possible for manufacturers to circumvent the PMA process for stents used in peripheral vasculature by clearing them through the 510(k) process and then having them be used off-label in peripheral vasculature. It was estimated that up to 90% of biliary-stent use was for off-label application in treating peripheral vascular disease (Bridges and Maisel, 2008).

evidence that the intended use documented in a 510(k) submission differs greatly from how the device will be used once it is cleared (FDA, 2010b); see Box 4-1 for a case study of biliary stents. To address that concern, CDRH has proposed seeking authority to consider an off-label use in determining the intended use of a device under 510(k) review (FDA, 2011a).

The FDA can take various steps to address off-label use that is the result of marketing practices of the sellers. If the off-label use, however, is the result of spontaneous medical practice, its authority over marketing is of no use. Furthermore, given the limited and problematic postmarketing surveillance of devices in general, accurately identifying adverse events or developing an evidence base on innovative indications for devices is not currently feasible. These factors complicate the FDA's ability to determine whether the potential off-label use of a device raises new types of questions about safety and effectiveness.

In general, the committee noted that there is a lack of data on off-label uses of 510(k)-cleared devices; in the absence of data, there is no basis for concluding whether such uses are, on balance, beneficial or harmful to the public.

Finding 4-5 There are no reliable tools for collecting data on the clinical use of and health outcomes related to devices cleared by

510(k) so that such data could become available for regulatory, healthcare policy, and medical decision-making purposes.

Finding 4-6 Insufficiency of information about how devices are used and perform once they are on the market adversely affects the ability of the FDA to evaluate devices' intended uses, indications for use, and substantial equivalence in a 510(k) review.

Class III Devices Remaining in the 510(k) Program

In the 1976 legislation, Congress directed that all preamendment devices classified in Class III undergo the PMA process on a timetable to be set by the FDA but could remain on the market pending completion of the review.³⁷ During the review period, new (postamendment) products of the same types as preamendment Class III devices would be permitted to enter the marketplace, essentially on the same terms as the preamendment devices.³⁸ Thus, the manufacturer of a postamendment device would not have to submit and obtain approval of a PMA before the manufacturers of a preamendment were required to. Instead, the manufacturer would submit a 510(k) notification demonstrating that its proposed product was “substantially equivalent” to a Class III preamendment device. Once PMA requirements were imposed, however, the use of the 510(k) process would terminate. It was a transitional tool for Class III devices.

The FDA has not completed the task given to it in 1976 to bring all devices classified in Class III under PMA review requirements. In the first decade under the 1976 amendments, over 80% of postamendment Class III devices entered the market on the basis of 510(k) submissions showing substantial equivalence to preamendment devices.³⁹ Congress has directed the FDA several times to finish the transition (FDA, 2011b).⁴⁰ Although the FDA has done so for many Class III device types, there are still 25 device types that remain eligible to enter the market through the 510(k) process. In 2009, the FDA implemented a five-step process called the 515 Program Initiative with the aim of completing the task (FDA, 2011b). As of April 2011, the FDA has assessed the risks and benefits associated with 21 device types (step 2 of the process) and has received and reviewed public comments

³⁷FFDCA § 515(b)(1), 21 USC § 360e(b)(1) (2006).

³⁸FFDCA § 513(f)(4), 21 USC § 360c(f)(4) (2006).

³⁹Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 344 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

⁴⁰SMDA, Pub. L. No. 101-629, 104 Stat. 4511.

on five device types (step 4 of the process). The agency has issued a final rule for one of the 26 device types (FDA, 2011c; GAO, 2011).

Finding 4-7 A number of Class III devices continue to be cleared through the 510(k) process rather than, as Congress has always intended, through the PMA process.

Types of 510(k) Submission

An applicant may choose from three types of premarket notification or 510(k) submission for marketing clearance, depending on the circumstances. Although there is no standardized 510(k) submission form, the FDA has a guidance document advising manufacturers on the format of submissions (FDA, 2005).

In addition to the traditional 510(k) submission, the FDA developed two submission types to streamline premarket notification. The *special 510(k) submission* uses components of the quality system regulations (QSRs) to address important modifications in a product already on the market that warranted a new 510(k) submission. The *abbreviated 510(k) submission*, as its name implies, is focused on reducing the length and complexity of a submission by allowing an applicant to show that its product conforms with agency guidance documents, special controls, or recognized performance standards as a means of showing substantial equivalence (FDA, 2010a). The two alternative review processes were developed through guidance rather than rule-making. A review of 510(k) submissions from 1996 to 2009 found that about 80% of submissions were traditional 510(k)s, 16% were special, and 3% were abbreviated (IOM, 2011).

Traditional 510(k) Submission

The traditional 510(k) submission can be used for all 510(k)-eligible devices. Although the FDA does not have a standardized format for submissions, it provides a recommended format in a guidance document (FDA, 2005). The information needed as part of this submission is described in 21 CFR Part 807 Subpart E and includes

- Statement of indications for use.
- 510(k) summary or 510(k) statement.
- Truthfulness and accuracy statement.
- Class II summary and certification.
- Financial certification or disclosure statement.
- Declarations of conformity and summary reports (abbreviated 510(k)s).
- Device description.

- Substantial-equivalence discussion.
- Proposed labeling.
- Sterilization or shelf life.
- Biocompatibility.
- Software.
- Electromagnetic compatibility or electric safety.
- Performance testing—bench, animal, and clinical.
- Information on the standards used and a statement that the submission conforms with them.
- Kit certification.

The first step in preparing any 510(k) submission is identification of a predicate device. As discussed above, it is possible to claim equivalence by using more than one predicate (FDA, 2010a). The demonstration of substantial equivalence is usually based on the information generated by performance testing. Given the wide array of products included in the 510(k) review program, there is a great deal of variation in the types of data that would be required.

The second step in preparing any 510(k) submission is identification of appropriate FDA guidance documents. Although guidance is not binding, it is likely to represent the FDA's thinking about the product type and to signal the kinds of questions that are likely to be asked by the review staff. In addition to device-specific guidance, the FDA has developed guidance on some cross-cutting device issues including biocompatibility, device software, and electromagnetic compatibility. Ideally, guidances provide submitters advance knowledge of the agency's concerns, allowing a submitter to anticipate likely questions and to provide appropriate evidence in the initial submission. A goal is to decrease the likelihood of requests from the agency for additional information.

Abbreviated 510(k) Submission

The abbreviated 510(k) submission is used only where device-specific guidance documents are applicable. Those documents communicate regulatory and scientific expectations both to FDA review staff and to industry. They identify the standards or guideposts that must be met for market clearance and provide methods for gathering and presenting such information. The use of the abbreviated 510(k) submission is based on the premise that if a well-recognized method for obtaining data relevant to the 510(k) decision-making process can be identified, the sponsor of a submission can comply with that method and give the FDA a summary report (FDA, 2010a). This submission type should streamline the process, simplify review, and decrease regulatory uncertainty.

All elements described in 21 CFR Section 807.87, as noted above for the traditional 510(k) submission, must still be provided to the FDA, but the use of a standardized method for obtaining these elements and a summarized report should allow more predictable and shorter review timelines. Normally, an abbreviated 510(k) submission would include the same sections as the traditional 510(k) submission. However, because of the important role of conformity with the existing guidance or standard, an abbreviated 510(k) submission should also include a specific section titled “Declarations of Conformity and Summary Reports.” Because a declaration of conformity is based on results of testing, the FDA believes that such a declaration of conformity cannot be submitted until testing according to the guidance or standard has been complete and shown to support substantial equivalence.

Although use of the abbreviated 510(k) submission is intended to simplify and expedite preparation and review, the deadline for agency action on the submission—90 days—remains unchanged.

Special 510(k) Submission

The Safe Medical Device Act of 1990 authorized the FDA to issue regulations requiring preproduction design controls. As a result of that legislative change, the FDA promulgated regulations for Class II and Class III devices and for select Class I devices as part of the good manufacturing practice (or quality system) regulations. The regulations may be described best as a systematic set of requirements and activities for the management of design and development. They include documentation of design inputs, risk analysis, determination of design outputs, test procedures, verification and validation procedures, and documentation of formal design reviews. Manufacturers must ensure that design-input requirements are appropriate so that a device will meet its intended use and the needs of the user population. The manufacturer must establish and maintain procedures for defining and documenting design outputs in terms that ensure conformity with design-input requirements.⁴¹

The special 510(k) submission is based on the premise that the rigorous application of design controls in addition to other 510(k) content requirements can be used to substitute for the traditional determination of substantial equivalence of legally marketed devices that are undergoing substantial modification and require new 510(k) submissions (FDA, 2010a). Manufacturers may submit a special 510(k) notification only when they are modifying their own 510(k)-cleared devices. Using this option, a manufacturer will conduct a risk analysis and then report on the verification and

⁴¹21 CFR § 820.30.

validation activities used to demonstrate that the modified device meets the design requirements.

The special 510(k) submission is intended for minor modifications of a device. It is not intended for products that are undergoing modifications of indications for use or labeling changes regarding intended use, for modifications that have the potential to alter the fundamental technology of the device, or for changes in materials that may raise safety or effectiveness issues (for example, use of new materials without a history of use in the same device type).

As an incentive to use this alternative pathway, the FDA seeks to act on a special 510(k) within 30 days of submission. This approach builds on well-established postmarket controls by incorporating them into the premarket review process. The weaknesses of this pathway are that it is limited to products that are undergoing controlled incremental change and has not been systematically analyzed.

EVIDENCE SUPPORTING 510(k) SUBMISSIONS

Data proving substantial equivalence have always been required for 510(k) submissions. However, because there were few special controls, guidances, and recognized standards for the program until 1984, the types and quality of data required were not well defined in its early years.

As discussed in Chapter 3, Class II devices may be subject to “special controls.”⁴² Some of these special controls can be in place either in the premarket period (such as performance standards and FDA guidelines), and others affect the device once it is on the market (such as postmarket surveillance). As of the end of 2010, only 140, or 15%, of all Class II device types were subject to special controls. There are no data on the breakdown of special controls that affect premarket review (Desjardins, 2010). Special controls generally are developed as part of the *de novo* process.

The primary mechanisms that the FDA has for communicating with manufacturers the evidentiary requirements needed to support a claim of substantial equivalence in 510(k) submissions are guidance documents and standards.

Guidance Documents

The FDA issues guidance documents or guidances on a wide variety of topics, including administrative procedures, such as the processing of submissions, and complex scientific requirements. The following discussion is about guidances focused on the evidence needed to support a substantial-

⁴²FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

equivalence claim. Guidance documents can be an important tool in advising manufacturers how to structure their 510(k) submissions to meet the FDA threshold for substantial equivalence. Guidances may also be important in making the review process more predictable and transparent.

There are limitations, however, on how guidances can be developed and used. In some cases, guidance documents include information on technical specifications, minimal engineering descriptions, and bench-level descriptions that would be sufficient to establish substantial equivalence. In other cases, they provide more extensive information on clinical studies that may need to be conducted to demonstrate substantial equivalence. Given the depth of information needed to develop guidance documents, the FDA needs to have sufficient information about the relevant product type to allow it to offer specific advice about how to gather information about a device's performance to support the submissions' claims of substantial equivalence.

A guidance document is the product of a long process involving both FDA and non-FDA input. Not all device types fall within the categories for which it is possible for the agency to develop guidance documents. As part of its internal review of the 510(k) program, the FDA reviewed more than 18,000 510(k) submissions and found that 63% lacked device-specific guidance (see Table 4-1) (FDA, 2010b).

Guidance documents “do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both” (FDA, 2009b). The FDA may choose to use guidance documents over regulations for a number of reasons, including because they are less burdensome to develop than regulations and they can provide a flexible, pragmatic regulatory approach (IOM, 2010).

As discussed in Chapter 3, the development of guidance documents is resource-intensive for the agency. The FDA has indicated that it takes 40 staff years to develop a mandatory performance standard (GAO, 1988). A non-binding guidance document, however, might require less work.

Standards

Standards, like guidance documents, are recommendations and provide specific protocols. Standards are developed by a number of national and international industry and scientific groups. Guidance documents may include references to standards that provide specific instructions for evaluating a particular aspect of a device. Standards become recognized by the FDA through a formal process of review and recognition (FDA, 2007b, 2007c). These recognized standards vary in their content but generally contain information that defines or describes their scope, provides definitions of terminology, lists referenced documents, and provides summaries of test methods, necessary apparatus, protocols, and necessary calculations.

TABLE 4-1 FDA Review Time by Availability of Guidance

Guidance Available	Mean FDA Days (Mean Total Days)	≤30 Days, % Completed (Number)	31–90 Days, % Completed (Number)	91–365 Days, % Completed (Number)	>365 Days, % Completed (Number)	All, % Completed (Number)
Yes	57.2 (93.0)	28.7% (1,937)	65.5% (4,424)	5.7% (387)	0.0% (3)	100% (6,751)
No	65.2 (139.5)	22.6% (2,617)	67.2% (7,786)	10.0% (1,162)	0.1% (16)	100% (11,581)
All	62.3 (122.4)	24.8% (4,554)	66.6% (12,210)	8.4% (1,549)	0.1% (19)	100% (18,332)

SOURCE: FDA, 2010b.

Conformity with standards can support a new device's claim of substantial equivalence to a predicate device. A manufacturer can state its adherence to consensus standards through a Declaration of Conformity to Standards (FDA, 2007a). Conformity with standards is not always a sufficient basis to support a substantial-equivalence finding. Conformity can, however, reduce the amount of documentation that a manufacturer must submit and may also reduce FDA review time.

The FDA and industry have raised concerns about the use of standards in the 510(k) review. The FDA reported inconsistencies in how standards are applied in 510(k) reviews and attributed the problem to insufficient training of review staff and unclear guidance to submitters. A submitter may not be using the most current standard, or may not be documenting use of the standard properly, or may be attempting to use a standard that is not appropriate for the device in question (FDA, 2010b).

Effect of Guidance Documents and Standards on Review Time

Although it is generally believed that use of guidance documents and standards simplifies the regulatory process, it is not clear how much effect they have on premarket review time (see Table 4-1). Devices for which there are guidances generally appear to undergo premarket review more rapidly than other devices. It is possible that the shorter review periods result from other variables in the review process, such as the relative familiarity of both the FDA staff and submitters with the device type, and might not be related to the existence or quality of the guidances themselves. In the absence of a quality-assurance program to rate the quality of submissions and reviews, it is reasonable to speculate but not easy to prove that guidance improves the work done by the sponsor or by the FDA in the 510(k) process.

Use of Clinical Data

The use of clinical data in the regulatory review process is defined by the enabling legislation, the regulations, and the FDA's implementation of the legislation and regulations. The FDA is able to request clinical data to determine if an indication of use falls within an intended use or if the agency determines that the 510(k) submission under review has new technologic characteristics relative to the predicate(s). The clinical data can be requested by the FDA only if necessary to determine that the new device is as safe and as effective as the predicate device(s). Moreover, the agency may not ask for scientific evidence greater than the "least burdensome" to answer the question.

In practice, clinical data play a very small role in the 510(k) process. The GAO found that in FY 2005–2007 about 15% of Class II and Class

III 510(k) submissions had new technologic characteristics (GAO, 2009b). The FDA found that only 8% of 510(k) submissions for non-in vitro diagnostic devices contain clinical data, and of those only 11% reference a predicate for which clinical data was provided. Less than 1% of non-in vitro diagnostic 510(k) submissions reference a clinical trial conducted under an approved Investigational Device Exemption application. The majority of 510(k) submissions for in vitro diagnostic devices contain some type of clinical information (FDA, 2010b).

There is no paradigm for devices that is similar to the Phase 0–IV clinical-trials paradigm used in the development, optimization, and registration pathway of drugs and biologics. Device trials are generally designated as either pilot or pivotal, and the specific clinical-trial attributes associated with each of these designations are not standardized or specified.

Some guidance documents focus entirely on preclinical device attributes, and others contain little guidance on clinical testing. For example, the *Guidance for Cardiovascular Intravascular Filter 510(k) Submissions* states (FDA, 1999) that

it is anticipated that human clinical investigations could be necessary in the development of a “new” vena cava filter to establish its equivalency to currently marketed filters. Such a study may also be necessary for a modified filter design. The need for such a study should be discussed with FDA prior to submission of an investigational device exemption (IDE) submission.

The guidance goes on to advise that “in those cases in which a study is deemed necessary, the sponsor should carefully consider the following items:

- the appropriate study design
- the study hypothesis
- appropriate sample size
- definitions of success and failure
- clinically relevant endpoints necessary for the demonstration of substantial equivalence.”

The guidance provides detailed information on the clinically relevant end points that might be necessary for the demonstration of substantial equivalence and labeling (for example, clinical indications and contraindications for use and warnings). It does not, however, define the other critical components of an appropriate study design, including how to determine an appropriate sample size and what characteristics and end points to use in defining success and failure. No guidance is available on determining clinically relevant issues, such as how to designate the primary aim, which in turn is a driving factor in such study-design decisions as sample size and secondary aims. There is also no guidance on identifying appropriate end

points for measuring the primary or secondary aims. In consultation with the FDA, the manufacturer determines what end points are necessary for the demonstration of substantial equivalence, what aspects should be subjects of clinical testing, or whether any clinical testing is needed. That consultation typically occurs in preinvestigational device exemption discussions between an applicant and the agency.

Although the preinvestigational device exemption meeting results in advice from the FDA on the submission, neither the applicant nor the agency is bound by it. An applicant can request a “binding letter of determination,” however, which obliges both parties to the terms in the letter. The agency reports that few applicants seek binding letters (IOM, 2010).

Both the FDA and industry have cited concerns about the lack of clarity as to when clinical, bench, and other types of information should be required to support the 510(k) submission. For premarket submissions that include clinical evidence, the FDA has described concerns about the variable quality of the studies and about the practice of compiling multiple studies, which may have different study designs (FDA, 2010b, 2010c). Medical-device industry representatives have stated that there is a lack of predictability with the 510(k) review regarding the types of clinical data needed to support the submission (IOM, 2010; Makower et al., 2010).

CDRH proposed developing guidance defining a subset of Class II devices, called “Class IIb” devices, for which clinical information, manufacturing information, or potentially additional evaluation in the postmarket setting would typically be necessary (FDA, 2011a).

Finding 4-8 There is no consistent approach for how the FDA determines the need for clinical data, the type of such data, and the manner in which such data, if available, are integrated into the decision-making process.

Variations in Review of 510(k) Submissions

Because the device types eligible for the 510(k) review process are immensely heterogeneous—with diverse risk profiles, applications of technologies, and relationships with identified predicates—there is an enormous variation in the complexity of 510(k) submissions reviewed by the FDA.

A new submission that has simple and obvious links to a predicate, that has a moderate risk profile, or that has a well-established history of device review may be assigned to a single member of the review staff, who will evaluate it and make a recommendation regarding substantial equivalence to the identified predicate. If unique software, statistical, or clinical issues are raised in the course of the review, consultations with software engineers, statisticians, or physicians may be sought.

A new submission that does not have simple and obvious links to a predicate, that has a higher risk profile, or that has a less established history of device review may be assigned to a multidisciplinary review team of regulatory scientists, often including a biologist, an engineer, a statistician, and a clinician and sometimes including an expert in software or epidemiology. Team reviews may be performed and recommendations developed about substantial equivalence.

In a complicated submission or a submission that raises new or controversial review issues, the FDA may use the expertise of members of its standing advisory panels to answer review questions or provide actual review. The submission is formally assigned to advisory-panel members outside the FDA who have the requisite expertise.

It is not uncommon for the FDA to request additional information to clarify or strengthen a submission during review. The FDA is limited in the types of information that it can request and how that information can be used. The new information can be used only to assess the submission's claim of substantial equivalence to the predicate(s). If the information needed is straightforward, a reviewer may simply call the submitter to make the request and will not need to put the submission on hold while waiting for a response. If the additional information needed is more extensive or complex, the reviewer will prepare a written letter and put the submission on hold.

Industry has questioned the transparency and credibility of the review process, however, when requests for additional information are seen as irrelevant to the intended clinical use or to the technology used. Industry representatives have also stated that requests made late in the review process are especially burdensome (FDA, 2010d). While the company is preparing a response to the FDA's request for information, the submission is not considered to be under active review, and the clock for review time is stopped. Responses to the FDA are usually requested within 30 days, but submitters may request an extension if more time is needed.

Another potential contributor to the variation in review time is the "least burdensome" provision discussed in Chapter 2. CDRH's Task Force on the Utilization of Science in Regulatory Decision Making found that FDA staff reported that industry perceives previous reviews as setting a precedent (FDA, 2010c). As new information about different devices and device types becomes available, the FDA may request different types of data from those of the past. Manufacturers sometimes see increased requests for data as unnecessary and contrary to the "least burdensome" principle (FDA, 2010d). Industry groups also contend that there is a lack of consistency and transparency in the FDA decision-making process and are concerned about lengthening review times, vagueness in the term *new types of questions*, and the burden associated with down-classifying devices. In particular, some industry groups have stated that the FDA asks for detailed

information on issues that are not clinically relevant or are obvious in light of underlying knowledge of the technology involved in the device. On the other hand, some in the scientific community believe that the agency has not asked even for rudimentary data that would have an important clinical impact (FDA, 2010d). As a result of those issues and concerns, CDRH has recommended that the “least burdensome” provision be more clearly defined (FDA, 2010c).

As mentioned before, CDRH is required to respond within 90 days of receipt of a 510(k) submission. In 2009, the FDA’s goal was to review 90% of 510(k) submissions within 90 days and 98% within 150 days (see Figure 4-2) (GAO, 2009b). That goal was met in previous years (see Table 4-1). Given the variability in the 510(k) submissions, CDRH staff report that review periods did not allow sufficient review of complex issues (FDA, 2010c). CDRH staff reported that they were unable to schedule and hold meetings, or respond to sponsors’ requests for information, because of the focus on submission review times (GAO, 2009a).

Data from CDRH’s 510(k) internal report show that the actual review times for most submissions are within the mandated limit (FDA, 2010b). Industry has noted that in an increasing number of submissions CDRH does

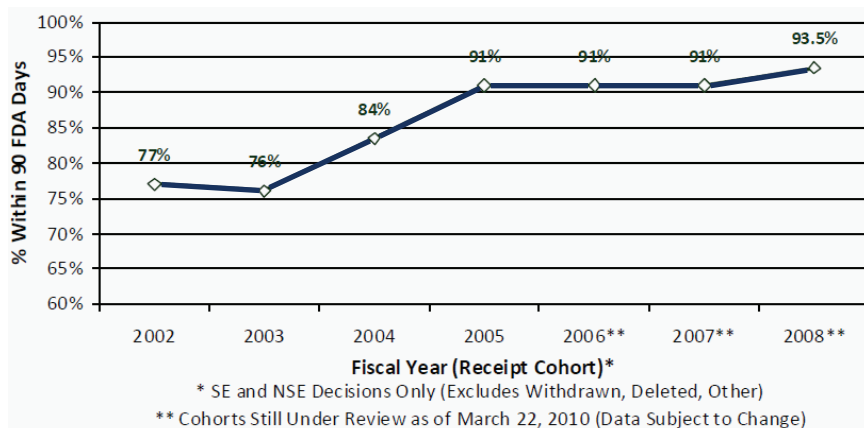


FIGURE 4-2 Percentage of 510(k) decisions within 90 FDA days, FY 2002–2008.
 NOTE: NSE, not substantially equivalent; SE, substantially equivalent; FDA Days are defined as the time during which a submission is under active review by FDA; “Submitter Days” is the time during which a submission is “on hold” pending the receipt of additional information requested by FDA; “FDA Days” and “Submitter Days” sum to the total length of time from initial FDA receipt of a submission until issuance of a decision.
 SOURCE: FDA, 2010b.

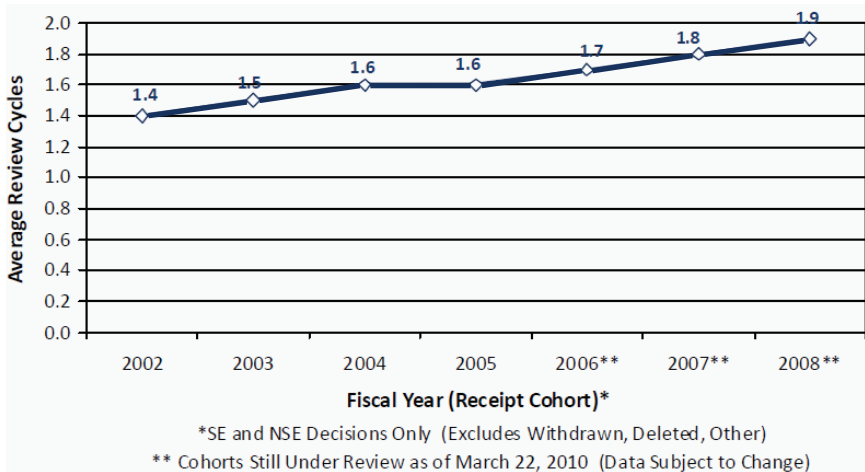


FIGURE 4-3 Number of 510(k) review cycles, FY 2002–2008.

NOTE: NSE, not substantially equivalent; SE, substantially equivalent.

SOURCE: FDA, 2010b.

not meet the mandates (FDA, 2010d). The FDA has stated that its resources are strained, given the complexity of submissions for innovative devices; these submissions require more FDA staff time and generally involve more review cycles (see Figure 4-3). It is possible to assume that complex 510(k) submissions are skewing the response times and increase review cycles, but without a detailed file review it is not possible for the present committee to determine whether this is the case.

Design Controls

The committee was given findings of two studies of the FDA's recall database (IOM, 2011). The studies assessed recalls associated with 510(k)-cleared products. Among the many measures assessed were the causes behind recalls of Class I 510(k)-cleared devices. Each study presented the recall data by reasons for the recall. The analysis conducted by Hall suggested that 55% of Class I recalls were related to postmarket issues and 45% to premarket issues (IOM, 2011). The analysis conducted by Maisel similarly concluded that about 57% of recalls were due to manufacturing process or device design (IOM, 2011). Given the results of those studies, it is clear that design issues and controls are worth examining more closely.

The FDA requires manufacturers of medical devices to implement

quality system regulations (QSRs),⁴³ which establish current good manufacturing practice requirements for “methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use.” The requirements are intended to ensure the safety and effectiveness of medical devices. 21 CFR Part 820 includes general descriptions and suggestions for establishing the following elements of a manufacturing process:

- A management subsystem.
- Design and development controls.
- Production and process controls.
- Corrective and preventive actions.

The regulation requires manufacturers to have the QSRs in place but provides only general guidance for its implementation, not device-specific guidance. The adoption of design control requirements was driven by studies performed by the FDA in the mid-1980s that evaluated the causes of recalls of medical devices. The studies revealed that almost 50% of recalls were attributed to the design and development phase of device manufacture. The FDA had no systematic means of tracking design and development issues. The controls described below would provide a paper trail for the FDA to follow if it inspects a facility involved in a recall. Despite the mandatory implementation of this requirement, device design is still responsible for almost half all Class I and Class II recalls (IOM, 2011; Shuren, 2010).

Manufacturers are required to have design and development controls for all Class II and Class III devices and for several types of Class I devices: any device automated with software, catheters for tracheobronchial suction, surgical gloves, protective restraints, a manual radionuclide applicator system, and a teletherapy radionuclide source. The ultimate implementation and approval of this management structure is left up to the manufacturer; the FDA provides only guidance and suggestions for implementation. A key element of the design-controls system is a list of documents that must accompany each device type produced by the manufacturer and must be maintained by the manufacturer and be available for review in the event of an inspection. The list includes the following:

- Design inputs.
- Design outputs.
- Design review before transfer from design to manufacturing.
- Design validation.
- Design verification.

⁴³21 CFR pt. 820.

- Design transfer.
- Design changes.

This collection of documents forms what is referred to as the device history record and forms a portion of a larger device master record. The master record describes the life of the device through design iterations, modifications, as well as other documents, and it should contain all relevant information about the design of the device. The master record is what the FDA reviews during an inspection. Manufacturers typically have multiple products and multiple models of each product, however, and each model has a device history record (DHR). An FDA investigator is generally able to review only a small portion of all the manufacturer's DHRs. It is not clear whether the documents required by the FDA are helpful in determining the reason for a recall or whether the documents provide the information necessary for improving the product or process to eliminate the reason for a recall.

CDRH can request that design-control information be included in a 510(k) submission (FDA, 2010b). The committee did not find data on how often design-control information is requested by CDRH staff as part of 510(k) reviews. CDRH noted in its preliminary internal evaluation that center staff have not received sufficient guidance and training in requesting this type of information from submitters or in when such information is necessary for deciding whether to clear a device (FDA, 2010b).

Device Labeling within the 510(k) Review

General labeling requirements are applicable to various types of devices. There is one general set for over-the-counter devices and another for prescription devices.⁴⁴ The prescription-device regulation, for instance, says that the label must “[bear] information for use, including indications, effects, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended, including all purposes for which it is advertised or represented.”⁴⁵ This general rule would apply to any prescription device, whether 510(k)-exempt, 510(k)-cleared, or PMA-approved. Moreover, in a few cases, the FDA has issued specific labeling requirements for particular devices.⁴⁶

Specifically for 510(k)-cleared devices, the 510(k) notification must include “proposed labels, labeling, and advertisements sufficient to describe

⁴⁴See Chapter 2 and CFR pt. 801.

⁴⁵21 CFR § 801.109.

⁴⁶E.g., 21 CFR § 801.435 (device-specific labeling for latex condoms).

the device, its intended use, and the directions for its use.”⁴⁷ The FDA is able to review the draft labeling and can negotiate with manufacturers on the text particularly for devices for which clinical study results are included. The final labeling is not cleared as part of the 510(k) clearance. The FDA, however, uses the proposed labeling to determine a device’s intended use for purposes of determining substantial equivalence. Moreover, the draft labeling of a 510(k)-cleared device may be changed at any time—even before initial marketing—not only without FDA approval but even without submission to the FDA. The FDA’s guidance includes information about when labeling changes should be included in a new 510(k) submission. 510(k) sponsors are obliged to “maintain in the historical file any labeling or advertisements in which a material change has been made anytime after initial listing.”⁴⁸ The FDA investigators might come across the change when conducting an inspection or when investigating a device problem. Otherwise, the FDA can be unaware of labeling changes made once a device is on the market.

In comparison, for PMA-approved devices, labeling is approved as part of the PMA approval process. After PMA approval, all proposed label changes that affect the safety and effectiveness of a device must be submitted to the FDA, and, with a few exceptions (for example, newly acquired information that warrants an immediate strengthened warning or new contraindication), all changes must be approved by the agency before they go into effect.

As discussed above, given that the FDA has relatively narrow mechanisms for addressing off-label use even when substantial risks are identified, it is often in the position of having to make decisions about substantial equivalence without complete information about how the device will be used once it is cleared.

DE NOVO PREMARKET REVIEW

The classification system introduced in the Medical Device Amendments of 1976 had provisions that designated all new medical devices that were introduced into the medical marketplace without predicates as Class III devices on the basis of their novelty regardless of risk. As a result, low-

⁴⁷21 CFR § 807.87(e).

⁴⁸21 CFR § 807.31(b). According to the FDA, material changes include any change or modification in the labeling or advertisements that affects the identity or safety and effectiveness of the device. These changes may include changes in the common or usual or proprietary name, declared ingredients or components, intended use, contraindications, warnings, or instructions for use. Changes that are not material may include graphic layouts, grammar, or correction of typographic errors that do not change the content of the labeling; changes in lot number; and, for devices whose biologic activity or known composition differs in each lot produced, the labeling that states the actual values for each lot.

risk or moderate-risk but novel devices would require a PMA application (FDA, 2010g).

The FDAMA remedied that cumbersome feature of classification by amending Section 513(f)⁴⁹ to provide a new mechanism to reclassify statutorily classified Class III devices. The new mechanism, referred to as the Evaluation of Automatic Class III designation (also called *de novo* or risk-based classification), allowed the FDA to streamline its approach to down-classification of devices that it deemed to be low or moderate risk. A device placed into Class I or Class II may be exempt from premarket review or be eligible for 510(k) review. A device placed into Class III will require a PMA application (FDA, 2010g).

Under the *de novo* process, the manufacturer must first provide a 510(k) submission. Once the FDA has issued a not-substantially-equivalent (NSE) letter, the manufacturer has 30 days to request a risk-based classification determination be made for the device. The request must describe the device and provide detailed information and reasons for any recommended classification. Not later than 60 days after the date of the submission of such a request, the agency must determine a classification by written order that places the device into one of the three statutory device classes:

- Class I device and may enter the market with no special control.
- Class II device for which a special control is required.
- Class III device type and is required to go through the PMA process.

Under the new classification provision, the FDA can assign new devices without predicates to Class I if the general controls are sufficient to provide reasonable assurance of safety and effectiveness and into Class II if special controls are needed to accomplish the same goal. In the absence of a predicate, substantial equivalence is no longer the operative review criterion. The submission must on its own (*de novo*) be found to be safe and effective. Once classified, the new product can serve as a predicate for future devices (FDA, 2010g).

For the reclassified Class II devices, the *de novo* process can be cumbersome and lengthy. As a part of the *de novo* review and classification, a special control needs to be developed and published before the classification is completed. In most cases, the device is new and no pre-existing special control is available. The FDA expressed concerns about the scientific challenge of crafting special controls to address risks associated with new devices and about the time required to develop guidances (FDA, 2010b, 2010d).

Manufacturers often know before they enter the 510(k) submission that a device will be found NSE and will require a *de novo* review. Many manu-

⁴⁹21 USC § 360c(f).

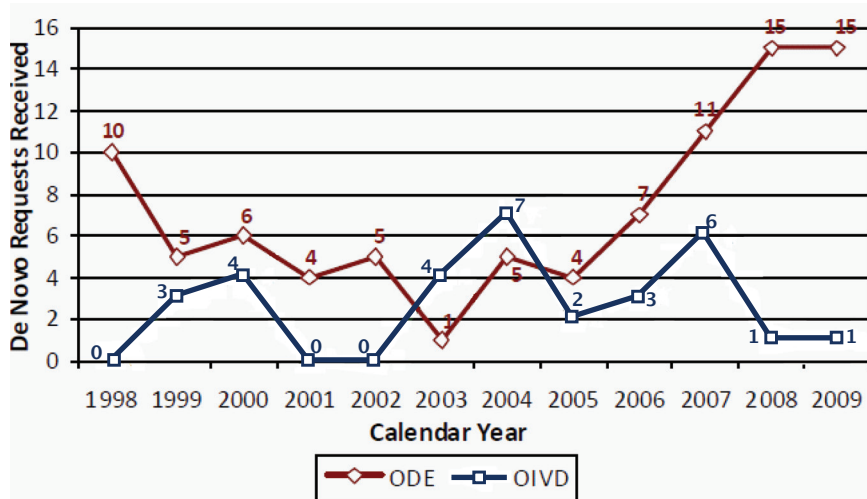


FIGURE 4-4 Number of de novo requests received, CY 1998–2009.

NOTE: ODE, FDA Office of Device Evaluation; OIVD, FDA Office of In Vitro Diagnostic Device Evaluation and Safety

SOURCE: FDA, 2010b.

facturers have preliminary discussions with the FDA regarding the types of information needed for the FDA to assess a new device's risk profile. That profile will be used to justify placement of the device into the appropriate classification (IVD Roundtable, 2002).

An industry-sponsored report indicated that the long timelines required to process de novo submissions detracted from the value of the program (Ladin and Imhoff, 2010). From the beginning of the de novo program in 1998 to 2009, the FDA received 119 de novo requests (see Figure 4-4) (FDA, 2010b). The FDA found that the average review time for in vitro diagnostic devices going through the de novo process increased from 261 days in 2005 to 448 days in 2009 (see Figure 4-5). There was a greater increase in review time for therapeutic devices, from 254 days in 2005 to 752 days in 2009 (see Figure 4-5) (FDA, 2010b). An industry-sponsored review of the de novo process found that only 54 de novo requests had resulted in clearance; 38 referred to in vitro diagnostic devices, 16 to therapeutic devices (Ladin and Imhoff, 2010).

Finding 4-9 Because of administrative constraints that make it burdensome for both manufacturers and the FDA, the de novo process has not met its potential as an alternative regulatory pathway for moderate-risk but novel medical devices.

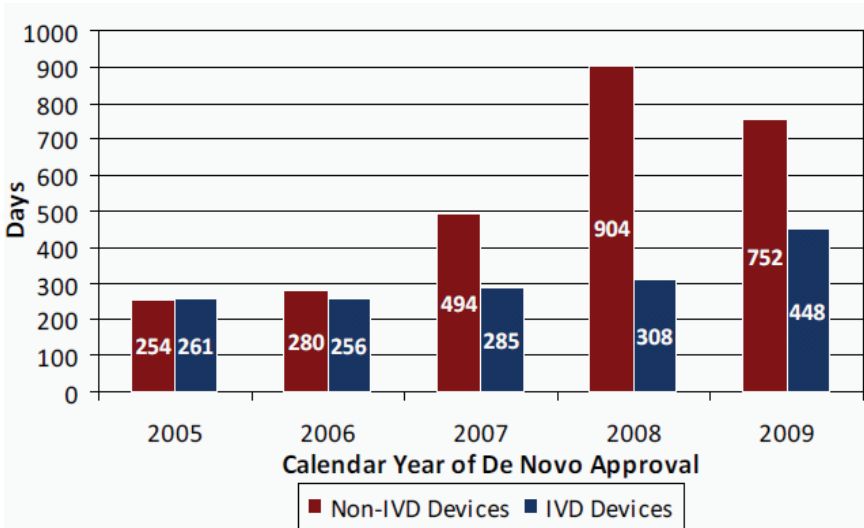


FIGURE 4-5 Average total time from 510(k) receipt to de novo approval, CY 2005–2009.

NOTE: IVD, in vitro diagnostic.

SOURCE: FDA, 2010b.

SUMMARY OF FINDINGS

- Finding 4-1 The 510(k) process determines only the substantial equivalence of a new device to a previously cleared device, not the new device's safety and effectiveness or whether it is innovative. Substantial equivalence, in the case of a new device with technologic changes, means that the new device is as safe and effective as its predicate.
- Finding 4-2 Current 510(k) decisions have been built on a chain of predicates dating back to devices on the market in 1976. Because data systems in the FDA are inadequate, the agency does not have the ability to trace the supporting decisions.
- Finding 4-3 The key regulatory terms *intended use* and *indications for use* are poorly defined and are susceptible to varying interpretations that lead to inconsistency in decision-making and create confusion among FDA staff, industry, Congress, the courts, and consumers.
- Finding 4-4 The 510(k) clearance process does not consistently recognize distinctions among devices cleared solely as tools, those

cleared for specific clinical applications, and general tools that also have specific clinical applications.

- Finding 4-5 There are no reliable tools for collecting data on the clinical use of and health outcomes related to devices cleared by 510(k) so that such data could become available for regulatory, healthcare policy, and medical decision-making purposes.
- Finding 4-6 Insufficiency of information about how devices are used and perform once they are on the market adversely affects the ability of the FDA to evaluate devices' intended uses, indications for use, and substantial equivalence in a 510(k) review.
- Finding 4-7 A number of Class III devices continue to be cleared through the 510(k) process rather than, as Congress has always intended, through the PMA process.
- Finding 4-8 There is no consistent approach for how the FDA determines the need for clinical data, the type of such data, and the manner in which such data, if available, are integrated into the decision-making process.
- Finding 4-9 Because of administrative constraints that make it burdensome for both manufacturers and the FDA, the de novo submission process has not met its potential as an alternative regulatory pathway for moderate risk but novel medical devices.

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5

Postmarketing Surveillance, Compliance, and Enforcement

Medical devices used both by professional healthcare providers and the public constitute a vital part of the healthcare environment. When used according to their manufacturers' guidance, devices are expected to be safe and effective. Given that, as discussed in Chapter 1, it is not possible to create a premarket review process that could completely ensure the safety of all devices before they enter the market, a strong surveillance system that monitors the safety of medical devices is essential. The identification of problems associated with a medical device can be an opportunity for various corrective actions, including improved device labeling, instructions for use or better user training, or, if appropriate, removal from the market.

This chapter reviews the current programs that the Food and Drug Administration (FDA) has in place, both passive and active, and some non-FDA surveillance programs that provide information on the safety and effectiveness of particular devices. It also examines how the FDA communicates information gathered through postmarketing surveillance activities to consumers, such as healthcare providers and the public.

The term postmarketing surveillance encompasses a wide array of programs, including medical device reporting by manufacturers and user facilities, third-party safety monitoring, and FDA–academic collaborations. The term postmarket surveillance refers to a specific activity defined by statute.

For medical devices, the FDA uses the term medical-device report (MDR) to encompass two types of reports—adverse-event reports are incidents resulting in a death or serious injury, and malfunction reports are incidents in which a device fails without an adverse event resulting.

Postmarketing surveillance is either “passive” or “active.” In a passive system, the regulator must depend on data from manufacturers and healthcare providers. The provision of data can be required by statute or be voluntary, but the role of the regulator is to collect and analyze the data that are provided. In an active system, in contrast, the regulator seeks information on adverse events, device malfunctions, and product effectiveness and takes advantage of opportunities to enhance data collection.

It is important to note that for most of the programs discussed below there is no reliable information about the number of devices (referred to as the denominator) on the market in clinical use. The lack of denominator information limits the ability to analyze potential safety concerns.

THE FOOD AND DRUG ADMINISTRATION'S CURRENT POSTMARKETING SURVEILLANCE ACTIVITIES

Mandatory and Voluntary Adverse-Event Reporting

Reporting requirements for the FDA are summarized in a 2009 Department of Health and Human Services (HHS) Office of the Inspector General (OIG) report (OIG, 2009), which states that

regulations require device manufacturers to report to the FDA (1) within 30 calendar days of acquiring information that reasonably suggests one of their devices may have caused or contributed to a death, serious injury, or malfunction and (2) within 5 working days if an event requires action other than routine maintenance or service to prevent a public health issue. Regulations also require user facilities, such as hospitals and nursing homes, to report deaths to both the manufacturer, if known, and the FDA within 10 working days. User facilities must report serious injuries to the manufacturers (or the FDA if the manufacturer is unknown) within 10 working days. User facilities must also submit annual reports to the FDA of all adverse event reports sent to manufacturers or FDA in the past year.

The vast majority of MDRs are reported by manufacturers; user facilities and others provide a small proportion of the reports received by the FDA (see Table 5-1). As a general matter, patients, caregivers, and healthcare professionals are not legally obliged to report adverse medical events. Consumers, such as healthcare providers and patients, can provide voluntary adverse-event reports to the FDA through its MedWatch program (FDA, 2009b).

TABLE 5-1 Medical-Device Adverse-Event Reports, 2003–2007

Type of Adverse-Event Report	2003	2004	2005	2006	2007
Manufacturer report	65,217	70,718	90,157	109,676	141,065
Percentage of total reports	90%	90%	92%	93%	94%
User-facility report	2,890	3,256	3,752	3,048	3,234
Percentage of total reports	4%	4%	4%	3%	2%
Other reports	4,759	4,610	4,552	5,571	5,911
Percentage of total reports	7%	6%	4%	5%	4%
Report total	72,866	78,584	98,461	118,295	150,210

NOTE: Other reports include FDA voluntary and distributor reports; percentages do not add to 100, because of rounding; 2005 and 2006 report totals do not include one report and five reports, respectively, because of missing data needed for analysis.

SOURCE: OIG, 2009.

Customary Data Sources

Two fundamental steps in all MDRs are recognizing that an adverse event or malfunction has occurred and then associating the event with one or more possible diagnostic or therapeutic interventions as causal or contributing factors. Identifying the event can be problematic for many reasons. Some problems with medical devices can become apparent immediately (for example, in a procedural situation in an operating room or an intensive-care unit), but in other cases problems can take a long time to be manifested. For example, a patient can have a procedure in a hospital, be discharged, and seek follow-up care for an emerging medical problem from a physician who does not associate the problem with the earlier procedure. In such situations, the event rarely is reported. Even when it is, the MDR often includes inadequate information about the situation or the device, which makes it difficult to link the device with the medical problem (IOM, 2011).

When a medical problem is suspected to have occurred in association with use of a medical device, a bioengineer or risk manager may or may not be available to assist in the assessment of the role and potential responsibility of the device and to take appropriate corrective action. When information is available about the role of the device in the event, healthcare facilities

are required by the Safe Medical Devices Amendments of 1990 to report the problem to the manufacturer if the problem is a device-related death or serious injury. In addition, the onset of some medical problems may be delayed, and the person using the potentially problematic device may no longer be a patient of a healthcare facility that is legally required to file an MDR.

Physicians increasingly use higher-risk devices, including implantable devices, in their offices where there is no legal requirement for them to report adverse events and device failures to the FDA. Voluntary reports made by healthcare providers have always made up a very small fraction of the reports received by the FDA. In 1993, the MedWatch program was established to improve reporting by device users, but it has had little impact: only 5.6% of reports were voluntary in 2004 (Greenfield, 2007).

The total number of events reported has increased steadily from 72,866 in 2003 to 150,210 in 2007 (OIG, 2009). Most initial reports of adverse medical events or device malfunctions lack critical information about the patient's medical history. The Office of the Inspector General found that of the more than 140,000 MDRs filed by manufacturers in 2007, 50% of the reports were missing device identification information, such as model numbers, and 11% were missing descriptions of the adverse event or device malfunction (OIG, 1990). Follow-up inquiries are essential to fill in the gaps in information. Manufacturers are required by the FDA to perform follow-up for the majority of reports received to obtain the missing information for the medical-device reporting system. The agency also requires manufacturers to trend adverse events for reporting.

Investigations of adverse events and device malfunctions can be hampered by refusals to provide further information on the part of the patient (who may now be involved in litigation for damages), the treating physician or the physician who used or implanted the device (who may become a defendant in litigation over alleged malpractice), and any healthcare facility involved (possibly also a defendant in litigation). The device itself might not be available for examination and testing. And the manufacturer of the device may become involved in product-liability litigation. There are other reasons, not related to liability or litigation, that also affect investigations, such as the unreimbursed cost to physicians and healthcare facilities of responding to requests for information.

The next phase depends on how the manufacturer handles the information. There are regulations governing timely review and maintenance of records. Manufacturers determine whether the information meets the threshold for a reportable event. They may categorize an event as user error (OIG, 1990). There have been instances in which manufacturers have underreported serious adverse events by not reporting them to their own regulatory staff (Bren, 2003). However, whenever any agent of a company

knows of an adverse event, the company is deemed to have knowledge and is required to report. A company that does not report is in violation of the law.

Manufacturers are required to report within 30 days if a device may have caused or contributed to a death or serious injury or, if a device malfunctioned and a death or serious injury could result if the malfunction were to recur, and within 5 days if a reportable event necessitates remedial action (other than routine maintenance or servicing) to prevent an unreasonable risk of substantial harm to public health. In 2007, 31% of the more critical 5-day reports were submitted late. Similarly, healthcare facilities submitted 39% of death and injury adverse-event reports late (OIG, 2009).

The timeliness of the FDA review of MDRs is also problematic. Fewer than one-third of MDRs were reviewed for the first time within 30 days, and fewer than half were reviewed within 60 days in every year from 2003 to 2007. Documentation of the reviews is also inconsistent, and this makes it difficult to track the agency's response to a specific event. Moreover, the FDA Office of Compliance does not link inspections to the adverse event that may have triggered them.

In addition to the previously described system for mandatory and voluntary reporting of adverse events and device malfunctions, summary reporting from industry provides an abbreviated method that relies on established codes for events that are well known and categorized. Although they allow trending, the summaries provide little in the way of new information, and may have outlived their usefulness in that they hamper the function of an already overloaded system. Similarly, the compliance of user facilities with required annual reports is difficult to assess because CDRH was able to provide fewer than half the reports to the HHS OIG (OIG, 2009). These reports can also be repetitive with respect to individually submitted events. Larry Kessler, former director of CDRH's Office of Surveillance and Biometrics, has suggested placing more emphasis on keeping the data in the manufacturers' quality-reporting systems (Kessler, 2010).

Data Management

Each MDR is entered into an event database by an FDA contractor and then undergoes triage by a safety analyst (generally a nurse or engineer working for the FDA) to look for a signal of risk of potential substantial harm. That screening is made more difficult by the low signal-to-noise ratio, the MDR reviewers' narrow experience with new technology, the absence of input to the reviewers by premarket staff more familiar with the device, and the sheer volume of reports, which exceeds the capacity of the current system (GAO, 2009b; IOM, 2011). Efforts to integrate the premarket and postmarket phases of review in a matrix approach have been proposed since 2005 (Schultz, 2007), but have proved difficult to sustain because staff were

in different facilities and had a heavy workload. But an integrated approach is important when reports of adverse events and device malfunctions appear shortly after introduction of a new device (Mehran et al., 2004).

As mentioned above, incomplete or poor quality MDRs makes it difficult to have an informed review of the problem. To address this issue, the FDA has safety analysts, who have relevant technological or clinical experience, attempt to contact reporters (for example, manufacturers, user facilities, or voluntary reporters) for additional information. In addition, safety analysts interact with each other for clinical or engineering expertise to more fully understand reports. All safety analysts attend internal FDA conferences or “group think” meetings where a decision on further investigation may be made (IOM, 2011). In addition, data-mining is being explored by a variety of staff as an additional tool that may help identify potential safety signals.

A rule proposed in August 2009 to require manufacturers to submit MDRs in an electronic format to allow more timely access to emerging adverse event information was met with resistance from industry, which called for a longer timeframe to implement the changes (Williams, 2010).

All signals are entered into a CDRH tracking system, but the main repository for adverse event reports is the Manufacturer and User Device Experience (MAUDE) database. This database is considered to be in need of reform because it is difficult to use and is not connected to any other CDRH database (FDA, 1999b). When William Maisel, former director of the Medical Device Safety Institute, attempted to use MAUDE for analysis of 510(k)-cleared devices, he found that the data were not well suited to analysis, because of incomplete reporting, insufficient information, and misclassification (IOM, 2011). Problems are also caused by the difficulty of aligning product-code assignments, but CDRH is trying to address this issue (FDA, 2010c). As discussed in Chapter 3, efforts to upgrade information technology (IT) facilities in CDRH in recent years have been less than successful, and, as documented in the FDA Center for Drug Evaluation and Research, the challenges are exacerbated by the lack of communication between IT management and users (Breckenridge Institute, 2006).

The Government Accountability Office (formerly the General Accounting Office) reported in 1989 and again in 2009 that the FDA was unable to manage its postmarket-surveillance responsibilities because of resource constraints, but the agency is also unable to estimate its current and future resource needs effectively because of a lack of reliable management information (GAO, 1989, 2009a).

Finding 5-1 The FDA's current postmarketing surveillance system relies on manufacturers, importers, and healthcare facilities to collect information, to investigate, and to make mandatory reports. Voluntary reporting of adverse events and device malfunctions

depends on patients, caregivers, and healthcare providers and facilities to identify them, to associate them with medical devices, and to submit reports.

Finding 5-2 The inadequacy of the current postmarketing surveillance system and the resulting lack of data make it impossible to confidently draw broad conclusions about the safety and effectiveness of products that are on the market.

Finding 5-3 Data collected with the current postmarketing surveillance system is not systematically integrated into the premarket review process.

Enhanced Surveillance

In addition to the general reporting requirements described above, the FDA conducts postmarketing surveillance via several other mechanisms: tracking of medical devices, the MedSun program, the MD EpiNet program, the Sentinel Initiative, and Section 522 surveillance studies.

Tracking

Tracking of medical devices by manufacturers can assist in notification to users of potential problems with a device and can facilitate recalls when necessary. The FDA requires tracking of 12 implantable devices and four other devices that are used outside hospitals. They include joint prostheses, implantable pacemakers, implantable defibrillator, mechanical heart valves, ventricular-bypass-assist devices, and implantable infusion pumps (Diehl et al., 2010). Manufacturers are expected to be able to provide within 10 days information about the location of devices that have been distributed to patients and within 3 days information about devices that are in inventory.

MedSun

Recognition of underreporting of adverse events led to the initiation in 2002 of a pilot program, the Medical Product Surveillance Network (MedSun), in which trained risk managers could recognize and report adverse events electronically. That direct connection with the clinical community in 350 hospitals, nursing homes, and outpatient diagnostic and treatment centers not only improved the quality of reports but also allowed the identification of “near-misses” (FDA, 2009a). In addition, focus networks were developed on specific subjects, such as LabNet, which focuses on hospital laboratories; TissueNet, on human cells, tissues, and their products;

SightNet, on ophthalmic devices; HomeNet, on device training and problems in the home environment; HeartNet, on electrophysiology laboratories; and KidNet, on neonatal and pediatric units. MedSun also conducts small sample surveys involving a small number of institutions to answer specific questions on product safety (FDA, 2009c).

A plan to implement real-time adverse-event reporting and establish pathways to interactive information exchange with healthcare providers is included in the FDA Strategic Plan for 2010 (FDA, 2010c). Additional plans include unspecified expansion of the MedSun nets, further evaluation of the regional representative pilot, and the incorporation of “large providers.” There are currently no resources allocated to implement those plans. The value of the approach is well demonstrated by the fact that 252 of the 350 MedSun facilities reported adverse events in 2007, accounting for 72% of all facilities that reported. In contrast, only 267 of the remaining thousands of other facilities reported adverse events in 2007, and that number has been declining (OIG, 2009). The regional representative pilot has established valuable linkages to healthcare providers and has led to more adverse-event reports. A 285% increase in reported medical-device concerns originating in pediatric specialties was demonstrated (Desjardins, 2011).

MD EpiNet

The MD EpiNet program, which began in February 2010, is intended to improve epidemiologic assessment of device performance by establishing an extramural network with 10 leading academic institutions that have experience with medical-device studies. The stated long-term goal is to “substantially contribute to the understanding of medical device performance and CDRH decision making, thereby improving public health, with an FY-10 focus on building a research infrastructure by linking CDRH with leading academic organizations in the country that have experience with medical device studies” (FDA, 2011b). As of May 2011, the Web site for the program lists the accomplishments as “establishment of a partnership development team to develop a research plan,” holding a “kickoff workshop with academic stakeholders” on April 30, 2010, and a workshop to discuss methodologic issues related to studying medical device performance on April 25, 2011, awarding contracts for administration of the program, and initiating pilot projects in the selected centers.

Sentinel Initiative

In 2007, Congress passed the FDA Amendments Act (FDAAA), Section 905 of which mandated that the FDA establish a postmarketing risk identification and analysis system to support active monitoring of postmarket-

ing drug safety. The FDA is responding to that mandate by developing the Sentinel system, which will harness clinical and administrative data held by existing health-information holders. Congress set a target for the system to include data on 100 million persons by July 2012 (FDA, 2011a). Although Section 905 of the FDAAA specifically authorized creation only of an active surveillance system for drugs, the FDA is using its general authority under Section 1003(b)(2)(c) of the Federal Food, Drug, and Cosmetic Act (FFDCA) to include medical devices in the Sentinel system. The Sentinel Initiative helps the FDA to fulfill its mission to “protect the public health by ensuring that . . . there is a reasonable assurance of the safety and effectiveness of devices intended for human use.”¹

The FDA has already received deliverables from 10 small contracts that address various issues related to system planning and design, such as data availability, system architecture, methods, legal and privacy issues, and stakeholder engagement. In addition, it has entered a cooperative agreement with the Brookings Institution to convene meetings and workshops on active medical-product surveillance issues. Early in 2010, the FDA awarded a 5-year contract to the Harvard Pilgrim Health Care Institute to develop a “Mini-Sentinel” pilot project, a scaled-down version of the Sentinel system. The Mini-Sentinel Coordinating Center is identifying appropriate data sources, developing a scientific framework for obtaining real-time data, and developing procedures to ensure data quality and privacy protection (FDA, 2010d). As of January 2011, the electronic health records of more than 60 million people have been added to the system (Behrman et al., 2011). To protect personal information, the system relies on a distributed network architecture that keeps identifiable health data behind the existing privacy firewalls of the participating data sources; only summary results are sent to the coordinating center. The mini-Sentinel and Sentinel planned activities are public-health activities and the Common Rule² does not require informed consent of individuals whose records are being examined (Rosati et al., 2010). These activities also fit within an existing exception to the Health Insurance Portability and Accountability Act privacy rule that allows disclosures to public-health authorities without individual authorization.³ The first year of the Mini-Sentinel effort focused on developing a data model common to data sources with an initial focus on claims data (Mini-Sentinel Coordinating Center, 2010). The Sentinel system is expected to expand and gain additional functionality over the next several years.

The Sentinel system will be able to provide data that are applicable to medical devices. For example, one Sentinel-related project identified,

¹FFDCA § 1003(b)(2)(C).

²Federal policy for the protection of human subjects (Common Rule) (implemented by the Department of Health and Human Services at 45 CFR § 46.101–124).

³45 CFR § 164.512(b)(1)(i).

described, and evaluated potential US orthopedic-implant registries that could participate in the creation of a national network of such registries as part of the Sentinel Initiative (Outcome Sciences, 2009). Data related to medical devices include rates of selected outcomes (for example, myocardial infarction and stroke), rates of infection, and rates of implant revision and reintervention. They also may be able to address functional status and quality-of-life outcomes. However, some 510(k)-related issues—such as software problems, manufacturing defects, out-of-box failures, misconnects and disconnects, packaging and labeling errors, and design-induced use errors—will not be captured (IOM, 2011).

As the FDA expands the scope of Sentinel to include medical devices, additional resources will be needed. Such an investment is expected to provide a rich source of clinical data from a much broader segment of the population and will prove cost-effective in the long term as adverse events associated with device use are identified and reduced (Behrman et al., 2011).

Section 522 Surveillance

Section 522 of the FDCA is a discretionary tool that allows CDRH to require manufacturers to perform specified postmarket clinical studies of Class II and Class III products (Gross and Kessler, 1996).⁴ Such studies are justified when device failure is likely to cause serious health consequences, if the device would be implanted for more than a year, or if it is a life-sustaining device used outside a health facility. A Section 522 study can be used as a condition of clearance for a Class II device that is expected to have substantial use in pediatric populations.⁵

Section 522 studies are generally focused on only one or two aspects of performance rather than on overall risk and performance, and the duration of each study is limited to 3 years unless a longer period is agreed to by the manufacturer. That period is too short for the discovery of some late safety or effectiveness problems. Even when studies are completed, they may not require reporting of all critical information, including mortality (Lenzer and Brownlee, 2010).

Unique Device Identifiers

The FDAAA requires the FDA to develop a system of unique device identifiers (UDIs) for distribution and use. The FDA has conducted several meetings and public workshops with key stakeholders, including label manufacturers, device manufacturers, and hospitals. The agency has also

⁴FDCA § 522(a)(1), 21 USC § 360l(a)(1) (2006).

⁵FDCA §§ 522(a)(1)(A)-(B), 21 USC §§ 360l(a)(1)(A)-(B) (2006).

conducted pilot activities on the effects of UDI implementation on FDA and labeler-organization business processes. It has also completed a pilot test of the usability and feasibility of a prototype UDI database (FDA, 2010h).

Manufacturers want to ensure that the FDA's standards are in alignment with those used in other regulatory systems. Advocates for the implementation of UDIs argue that UDIs could substantially improve the FDA's ability to track medical devices once they are on the market. Implementation of a comprehensive UDI system could also reduce medical device-related errors, improve the quality of MDRs, facilitate device recalls and tracking, standardize device nomenclature among administrative databases and clinical registries, identify device use and compatibility issues, and enhance device postmarket surveillance (ERG, 2006).

Finding 5-4 Several tools, such as device tracking and Section 522 surveillance studies, are available to the FDA to improve postmarketing surveillance, but they are used only sparingly.

Finding 5-5 The FDA has postmarketing surveillance programs—such as MedSun, MD EpiNet, and the Sentinel Initiative—that are scientifically promising, but achieving their full promise will require a commitment to provide stable, adequate resources and will require resolution of various technical issues, such as unique device identifiers.

Compliance and Enforcement

When there is a problem with an FDA-regulated product, the agency's initial effort is to work with the manufacturer to have it corrected voluntarily. If that fails, a number of legal remedies are available: the manufacturer can be asked to recall the product, federal marshals can be used to seize the product, or an imported product can be detained at the port of entry until the problem is corrected. In addition, individual company officers that deliberately violate the law can be prosecuted, with the possibility of criminal penalties. Chapter 3 contains a detailed description of the postmarket regulatory authorities that are available to the FDA.

Each center has an office of compliance that ensures compliance with regulations for premarket or postmarket studies and for manufacturing and labeling. The Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) is responsible for both premarket review and postmarket enforcement for in vitro diagnostic devices. For non-in vitro diagnostic devices, the Office of Device Evaluation (ODE) oversees premarket review, but the compliance function resides in the Office of Compliance (OC). Inspections can be made at any establishment where devices are manufactured, processed,

packed, used, or implanted or where records of results are maintained. In addition, during inspections of manufacturers, inspectors review the manufacturers' procedures and records pertaining to reported adverse events and customer complaints. Since 2004, when there were 2,936 such foreign and domestic inspections, the number has steadily declined; there were 2,353 inspections in 2008 (Williams, 2010). Even when manufacturing problems are reported, the lack of effective action can lead to serious consequences in some cases (Lenzer, 2009).

Each compliance office works closely with the Office of Regulatory Affairs, which is responsible for the regulation of 124,000 establishments that produce, store, and transport an estimated \$1 trillion dollars worth of medical products. Consumer safety officers and inspectors conduct about 22,000 inspections a year and also monitor clinical trials (Williams, 2010).

Warning Letters

When there is a violation of the laws that the FDA enforces related to a device, process, or practice, the initial communication is likely to be a warning letter to a responsible person, manufacturer, or facility to take appropriate and prompt action. Warning letters are informal and advisory but are available to the public on the FDA's Web site and usually receive the attention of the news media. The number of warning letters from CDRH has steadily declined from 528 in 2000 to 136 in 2009 (Williams, 2010). In addition to a warning letter, the FDA may also issue a safety alert in the form of a "Dear Doctor" letter to warn healthcare providers and consumers of the risk associated with a device.

The effect of a warning letter varies. If the letter is directing a manufacturer to stop promoting a medical device for a specific indication, it can be corrected immediately. If the letter is related to a manufacturing issue, however, the process could take several months or even years to resolve. The FDA has the authority to use warning letters to block device PMA approvals, but generally not 510(k) clearances because of a 1997 legislative enactment. The FDA may withhold clearance of a 510(k) submission for manufacturing issues only if there is a "substantial likelihood" of a serious risk to health from the specific product because of a specific good manufacturing practice violation.

Recalls

Under the current FDA definition, a recall is any action to remediate a risk posed by a product already transferred from the manufacturer's control to others (such as wholesalers, retailers, end users, or patients). Actions that may be considered recalls include a software patch, a sticker on the package,

a Dear Doctor letter, a Dear Patient letter, servicing in the field, and a revision of labeling to add warnings or clarify instructions. Recalls of medical devices are usually conducted voluntarily by manufacturers on their own initiative or after negotiation with the FDA. Manufacturers and importers are also required to report to the FDA any voluntary correction or removal of a device undertaken to reduce a health risk posed by the device.⁶ Occasionally, if a manufacturer or importer fails to recall a device that poses a risk to health, the FDA may issue a formal recall order to the manufacturer.⁷

Recalls are classified by the FDA according to the degree of hazard, which is based on injuries or deaths that have occurred, the likelihood of occurrence, the population exposed, and immediate and long-term consequences:

- Class I recalls are the most serious and are reserved for situations in which there is reasonable probability that use of or exposure to a product will cause serious adverse consequences or death.
- Class II recalls are for situations in which a product may cause temporary adverse health consequences but in which there is the possibility of severity great enough to have irreversible consequences.
- Class III recalls are for situations in which use of or exposure to a product is not very likely to cause adverse health consequences but the likelihood is great enough to justify recall.

Class II recalls make up the largest recall class and have increased progressively from 1,235 in 2004 to 2,178 in 2008 (Williams, 2010).

Off-label use of a device—its use in a manner different from that of its original approval—is not regulated by the FDA but can lead to a recall. That situation occurred in 2004 when insertion of biliary stents to treat arterial disease had adverse outcomes (FDA, 2011d); in this case, it was the instructions for use that were recalled, rather than the devices themselves.

Limitations of Recall Data

The committee explored FDA recalls of medical devices as potential indicators of their safety. A recall study can be a useful tool for identifying the point in the product life cycle at which a problem is occurring, such as problems with device design or with the manufacturing process. Recall studies have limitations, however. FDA-initiated recalls may not fully reflect the safety, or lack thereof, of devices in clinical use. Without a robust postmarketing surveillance system that can detect safety problems dependably, the absence of a recall can mean that there were no safety problems

⁶21 CFR pt. 806.

⁷21 CFR pt. 810.

BOX 5-1**Case Study: Cardiovascular Intravascular Filters**

There have been reports of device malfunctions and adverse events related to permanent and temporary (retrievable) intravascular filters (McCowan et al., 1992). Data in multiple reports in the scientific literature make a strong case for believing that the adverse-event and device-malfunction rates of permanent and temporary filters as cataloged by the FDA understate actual rates (Dorfman, 1990; FDA, 1999a, 2010g; Nicholson et al., 2010). In August 2010, the FDA issued a medical alert noting that retrievable inferior vena cava filters could move or break and perhaps cause serious problems (FDA, 2010e). The FDA cited malfunction rates that are much lower than rates cited in nearly contemporaneous reports in the scientific literature (Dorfman, 1992; FDA, 2010g; Nicholson et al., 2010). No recall has been issued.

with a device or that the device's safety problems went undetected. The study of recall data is hampered by the lack of reliable denominator data. Recall rates often do not correlate with MDRs or with adverse-event rates reported in the scientific literature. Box 5-1 presents an example of the lack of a relationship among data in the scientific literature, MDRs, and recalls.

Two studies that evaluated recall rates of 510(k)-cleared and PMA-approved devices were presented at a July 2011 workshop hosted by the committee (IOM, 2011). William Maisel (formerly of the Medical Device Safety Institute) reported that recalls affected 510(k)-cleared devices 400–500 times a year from 2003 to 2009 (more than 48,000 devices were cleared through the 510(k) pathway in 1996–2009). He found that the annual rate of recalls of 510(k)-cleared devices was highest within the first 4 years after clearance (1.4–1.6%) and that the rate decreased after 5–6 years (to 0.9–1.1%). The reasons for recall included problems with the manufacturing process, including storage, labeling, and maintenance (28.8%); failure of a device to perform as intended despite meeting design specifications (28.4%); problems with nonconforming materials or components (16.3%); adverse changes in specifications or procedures (11.9%); employee error (7.1%); and miscellaneous (7.5%). The majority of recalls for the period reviewed (2003–2009) were of devices that went through the traditional 510(k) clearance process. Devices most likely to be recalled had a larger number of predicates (more than six), went through the special 510(k) clearance process, went through third-party review, were life-sustaining, or were Class

III devices. Three-fourths of recalled devices that were 510(k)-cleared were recalled a single time. Maisel also examined MDRs and recalls of 510(k)-cleared devices. He found that 41.8% of MDRs on 510(k)-cleared devices were associated with devices that were subject to recall.

Ralph Hall, University of Minnesota Law School, conducted the second study evaluating recall data on 510(k)-cleared devices. He presented his findings to the committee at its July 2011 workshop (IOM, 2011). Hall's review of Class I recalls for the years 2005–2009 showed that 55% were related to postmarket issues. He suggested improving quality system regulations with better design controls, bench testing, and preclinical studies.

Medical-device recalls also were assessed in a third study, which analyzed FDA recall data from 2005 to 2009 (Zuckerman et al., 2011). For that period, 113 Class I recalls were identified. Of those, 21 were of devices approved by the PMA pathway, 80 were cleared by the 510(k) pathway, 8 were exempt from FDA regulation and had only to be registered, and 4 were counterfeit devices or categorized as “other” and did not go through approval, clearance, or registration. Of the recalled devices, 35 were cardiovascular devices (the largest category), and 23 of them had gone through the 510(k) clearance process; 13 of the 23 were Class III devices.

The committee concluded that these studies, while offering insights, have little utility in assessing the ability of the 510(k) process to assure safe products reach the market. Recall data lack strong denominator information, or even a consensus on the proper denomination group. Classification of recalls may be imprecise as well. Some important problems with 510(k)-cleared devices do not rise to the level of a Class I recall (Kessler, 2010). As noted above, there is a lack of correlation between MDR data and recalls, and moreover, data in MDRs can be incomplete and insufficient. Jeffrey Shuren, director of CDRH, commented that most recalls of 510(k)-cleared devices are Class II recalls, which have the potential to have a serious effect on public health and safety (Shuren, 2010).

NON-FOOD AND DRUG ADMINISTRATION POSTMARKET DATA-COLLECTION EFFORTS

Some medical-device postmarket data-collection activities are outside the FDA. They are in four major categories: postmarketing surveillance programs, administrative databases, clinical registries, and electronic health records. The FDA has partnerships with academic institutions, federal agencies, and professional medical societies. Although current collaborations are focused on devices approved through the PMA process, the partnerships provide a model of potential mechanisms for the collection of postmarketing data on devices cleared through the 510(k) process. Although non-FDA data sources have several strengths and limitations, linking the various

data sources could potentially assist the FDA in postmarket surveillance of medical devices. The development of a network of existing administrative databases, electronic health records (EHRs), and clinical registries may enhance the FDA's ability to assess longitudinal device outcomes.

Postmarketing Surveillance Programs

The Department of Veterans Affairs (VA) Cardiovascular Assessment, Reporting, and Tracking (CART) system is a cardiovascular-disease surveillance program that is integrated into VA's Computerized Patient Record System. The CART program is used by VA for quality, management, patient-safety device surveillance, and research (IOM, 2011). VA shares with the FDA information collected through the CART program on signals or unexpected problems with devices reported by clinicians. The strengths of this program include the level of clinical, patient, device, and outcome data; VA-wide collaboration; integration of data collection into work flow; clinical tools, such as real-time report generation; VA-wide standardization; e-mail reporting of complications; monthly site reports; national reports; and Veterans Integrated Service Network reports (IOM, 2011). Although it is successful for cardiovascular surveillance within the VA system, the utilization of this system in other organizations that have different electronic health record (EHR) systems and levels of integration may limit generalizability. Expansion of this model to other devices in the VA system may provide an additional data source for the FDA's postmarket surveillance efforts. It should be noted that this effort is restricted to devices associated with a small number of clinical diagnoses and procedures. Thus, a small number of personnel need to be trained and integrated into the effort. Expansion of this model to other disease states and device types, even within the same institution, may bring additional challenges.

Another surveillance program is the Data Extraction and Longitudinal Trend Analysis (DELTA) system. DELTA is a software system that supports automated postmarket surveillance of cardiovascular devices (IOM, 2011). The software provides signal detection of adverse events with a generic structure, multiple analyses, and statistical applications for risk assessment (IOM, 2011). DELTA-detected signals must be followed up with interpretation and further investigation. Although successful in cardiovascular signal detection, the system has not yet been applied to other medical specialties. The FDA, which provides research support for the DELTA project, is exploring application of the DELTA system to orthopedic-device surveillance.

Administrative Databases

Several existing administrative databases could be used by the FDA for postmarket data collection on medical devices. For example, the FDA has used the Centers for Medicare and Medicaid Services (CMS) database to study the safety of implanted surgical mesh (IOM, 2011). The FDA's MD EpiNet program has been established to leverage the use of existing administrative databases in combination with internal FDA premarket and postmarket surveillance studies (IOM, 2011). Extended use of CMS data could enhance the monitoring of new technologies in people 65 years old and older from a wide variety of healthcare facilities (Mehran et al., 2004) and has the potential for longitudinal device monitoring (Normand et al., 2010). Although CMS data are related to a large, representative sample of the older patient population, limitations in device monitoring include restriction in age range, lack of laterality, sparse clinical and implant data, and various limitations associated with administrative database coding.

Other potential databases for assessing medical-device performance include the Nationwide Inpatient Sample (NIS) (HCUP, 2010), the National Hospital Discharge Survey (NHDS) (CDC, 2010), and state hospital-discharge databases. The NIS and the NHDS provide an opportunity to assess performance of classes of devices or specific procedures, but they lack detailed device information, such as manufacturer and catalog and lot numbers, that are necessary for evaluating the performance of specific devices. In addition to the need for linking devices to procedures or diagnosis codes, these databases contain few outpatient data and availability of recent data (Torrence, 2002).

Clinical Registries

Domestic and international clinical registries provide additional opportunities for postmarket data collection. Registries are defined as “organized systems that use observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serve one or more predetermined scientific, clinical, or policy purposes” (AHRQ, 2010). The strengths of patient registries include known denominators and the extent of clinical and implant detail necessary for assessing device outcomes. In addition, registries can provide large samples for detecting rare adverse events and provide an alternative when randomized clinical trials are not practical, ethical, or feasible (AHRQ, 2010). Another benefit of clinical registries is the real-world assessment of medical-device performance in people who are in different care settings and have varied comorbidities.

Medical professional groups, such as the American College of Cardiology (ACC), have developed national clinical registries, including the

National Cardiovascular Data Registry for implantable cardioverter defibrillators (NCDR ICD). The NCDR ICD is an example of a successful registry that collects clinical, implant, and outcome data and allows risk stratification (IOM, 2011). NCDR ICD tracking is mandated by CMS, and this mandate results in high participation by hospitals. Other ACC registries—for example, CARE for carotid artery stenting and endarterectomy procedures and ACTION–Get with the Guidelines (GWTG) for acute myocardial infarction—have lower participation because of the lack of incentives (IOM, 2011). The FDA has established relationships with ACC and other medical professional groups to collaborate in medical-device assessment. Professional-society registries, such as the ACC NCDR, provide an opportunity to capture the device and clinical data needed for risk adjustment and device assessment. Low participation, lack of longitudinal assessment, and the cost of implementation of these registries are potential barriers in expansion to other medical devices. Another potential limitation of societal registries is the lack of standardization among specialty registries that track the same medical devices. In those cases, there is no standard for such factors as data collection, nomenclature, and performance thresholds.

In addition to professional-society registries, institutional, regional, and national device registries could be used for collecting postmarket information on medical devices. For example, in orthopedics, there are several total-joint-replacement registries, such as the University of Massachusetts Global Orthopedic Registry, the Harris Joint Registry, the HealthEast Orthopedic Joint Registry, the Hospital for Special Surgery Center for Education and Research on Therapeutics Total Joint Replacement Registry at Weill Cornell Medical College, the Kaiser Permanente National Total Joint Replacement Registry, the Mayo Clinic joint-replacement database, the MaineHealth Total Joint Replacement Registry, the Rush University Medical Center Joint Registry, and the Virginia Joint Registry (Outcome Sciences, 2009). The FDA has evaluated the quality of those registries and established collaborations to assess the safety and effectiveness of total-joint-replacement devices.

Internationally, there are numerous national orthopedic registries, including the Swedish, Norwegian, and Australian joint-replacement registries. Findings from those registries have initiated recalls and advisories in the United States. For example, a recent US DePuy ASR XL Acetabular Hip System and DePuy ASR Hip Resurfacing System recall was influenced by findings from several international total-joint-replacement registries. Problems associated with these devices were first identified in the Australian registry, which detected a higher than expected revision rate for these devices in 2007. The findings from the Australian registry and similar findings from the National Joint Registry of England and Wales prompted a recall of these devices. The ASR recall demonstrates the potential of implant registries for

postmarket data collection. Recognizing the importance of device registries, the FDA is exploring the development of the scientific infrastructure for a consortium of existing domestic and international orthopedic registries.

Registries may provide detailed clinical and device information, but they also have limitations, such as losses to follow-up, which adversely affect longitudinal tracking and potentially introduce selection bias in that they are not entirely random. Participation is also a challenge for some registries when incentives are lacking. Some clinical registries were developed for specific diseases or conditions, and this can limit their use for a wide variety of medical devices. And clinical registries are resource-intensive to develop and maintain. Despite the challenges associated with registry development, implementation, and maintenance, several regional and national efforts are under way in the United States to track orthopedic devices, such as total joints. The American Academy of Orthopaedic Surgeons American Joint Replacement Registry, a California state registry effort, and an Agency for Healthcare Research and Quality multicenter registry project may be able to assist the FDA in future postmarket surveillance efforts.

Electronic Health Records

EHRs are another possible means for monitoring medical-device performance. EHRs provide an opportunity to collect data prospectively at the point of care, integrate device information into the workflow, and assess clinical and device granularity needed for risk adjustment. Despite the potential for EHRs in medical-device postmarket surveillance, there are several challenges to implementation. First, EHRs have not yet been fully integrated into all health systems (DesRoches et al., 2008; Jha et al., 2009), although the use of electronic records by hospitals and healthcare professionals is expected to increase rapidly with resources allocated by the American Recovery and Reinvestment Act of 2009. In addition, there are more than 40 EHR systems, and they do not have standardized data-entry fields and formats. Most important, medical devices are not monitored in a consistent manner. Many EHRs lack discreet data fields for efficient data extraction and analysis. Concerns regarding privacy, security, and confidentiality are other challenges to the use of data from EHRs in postmarket surveillance. For EHRs to be used for future device monitoring and surveillance, data definitions and formats must be standardized, interoperability and data-exchange issues addressed, and privacy, regulatory compliance, and confidentiality ensured. The implementation of UDIs could substantially improve the FDA's ability to track implants by using EHRs and standardizing device information among EHR systems.

Finding 5-6 Existing non-FDA device data sources could enhance current passive FDA postmarketing surveillance systems but are variably used by the FDA and providers.

Finding 5-7 The lack of standardization in clinical and device-specific data among existing non-FDA data sources and insufficient detail in administrative and clinical health records impede the evaluation of the performance of medical devices.

COMMUNICATING WITH CONSUMERS

When a problem with a medical device warrants action, communicating essential information to healthcare providers and the public is challenging for the FDA. Recalls and public-health notices are posted on the FDA's weekly enforcement report (FDA, 2011e). A report is publicized when the FDA believes that there is a potential for serious public hazard. But neither safety alerts nor recalls are distributed to appropriate recipients in a timely fashion (GAO, 1998, 2007). Recall notices may be sent to a person ordering supplies, to a loading dock, or to a billing department. Confusion about the appropriate course of action may occur when a recall notice is received. Poor communication among providers, industry, and the FDA was previously noted by the Institute of Medicine in a report that focused on device problems in pediatric patients (IOM, 2005).

Several third-party organizations offer services to ease communication between the FDA and consumers about recalls and other FDA notices, alerts, and reports. For example, the Emergency Care Research Institute is a nonprofit corporation that contracts with hospitals to provide advice on appropriate responses to FDA communications (Mantone, 2006). Commercial online tracking systems for recalls (for example, RASMAS, a recall management service for the healthcare sector [RASMAS, 2011]) also are available from other organizations.

Delays in communication of recall notices leave patients at risk and hospitals with medicolegal liability. In 2002, contaminated bronchoscopes remained in use for more than 3 months after a warning was issued, and the blame for later infections was directed at both the manufacturer and the FDA (Patterson, 2002).

The Transparency Initiative established in 2009 was intended to make public access to FDA information more widely available (FDA, 2011c). The initiative includes providing information about regulated products to the public through the CDRH Web site and making public the results of Section 522 and other postapproval studies. The site was launched in April 2010 and provides access to safety alerts, public-health notices, MedSun reports, and the MAUDE database. In the first month of its availability, however, it

received only 46 comments despite a readily accessible response form and request for feedback (FDA, 2010b). In recognition of existing limitations, a recommendation from the CDRH Task Force on the Utilization of Science in Regulatory Decision Making was to use new science and available clinical experience to communicate necessary changes in device manufacturing and labeling (FDA, 2010a). Such communications might include letters to industry, public notices, ordering of a Section 522 study, or modifying premarket requirements.

The process that has proved most effective in generating reliable MDRs also has advantages for communication of recalls (Kessler, 2010). Under the MedSun program, a trained risk manager serves as the point person for direct communication of recall information. That person can use hospital information systems to communicate risk notices to the appropriate personnel rapidly and then ensure that the appropriate corrective actions take place. The committee believes that a major improvement in the removal of affected devices from the market could result from the proposed UDI system mandated by Section 519(f) of the FDAAA, depending on how such a system is implemented. This system would permit not only more rapid analysis and collation of adverse event reports but also would focus on removal of only the affected devices when necessary. The proposed UDI rule is being drafted (FDA, 2010f), and the UDI system is scheduled to be fully implemented in 2013 (FDA, 2010c).

SUMMARY OF FINDINGS

- Finding 5-1 The FDA's current postmarketing surveillance system relies on manufacturers, importers, and healthcare facilities to collect information, to investigate, and to make mandatory reports. Voluntary reporting of adverse events and device malfunctions depends on patients, caregivers, and healthcare providers and facilities to identify them, to associate them with medical devices, and to submit reports.
- Finding 5-2 The inadequacy of the current postmarketing surveillance system and the resulting lack of data make it impossible to confidently draw broad conclusions about the safety and effectiveness of products that are on the market.
- Finding 5-3 Data collected with the current postmarketing surveillance system is not systematically integrated into the premarket review process.
- Finding 5-4 Several tools, such as device tracking and Section 522 surveillance studies, are available to the FDA to improve postmarketing surveillance, but they are used only sparingly.
- Finding 5-5 The FDA has postmarketing surveillance programs—such as MedSun, MD EpiNet, and the Sentinel Initiative—that are

scientifically promising, but achieving their full promise will require a commitment to provide stable, adequate resources and will require resolution of various technical issues, such as unique device identifiers.

- Finding 5-6 Existing non-FDA device data sources could enhance current passive FDA postmarketing surveillance systems but are variably used by the FDA and providers.
- Finding 5-7 The lack of standardization in clinical and device-specific data among existing non-FDA data sources and insufficient detail in administrative and clinical health records impede the evaluation of the performance of medical devices.

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6

External Factors That Affect the Medical-Device Regulatory System

Chapters 3, 4, and 5 review and analyze how the Food and Drug Administration (FDA) regulates medical devices. However, that regulatory process does not exist in isolation. It is a part of a broad landscape consisting of such additional factors as the increasing complexity of medical devices, the process of innovation, the business environment in which medical devices are developed, and the international medical-device regulatory arena. This chapter explores those factors and how they have the potential to affect the regulation of medical devices in the United States.

THE GROWING NUMBER AND COMPLEXITY OF MEDICAL DEVICES

The number of 510(k) submissions to the FDA varies from year to year (see Figure 6-1). In 1976, fewer than 1,000 510(k) submissions were received by the FDA's Center for Devices and Radiological Health (CDRH). The number of submissions reached about 7,000 in 1989 (in part because of a change in the status of examination gloves from 510(k)-exempt to non-exempt). In 2009, about 4,000 submissions were received (FDA, 2010a). The number of 510(k) submissions declined most dramatically from the early 1990s to the middle 2000s. At least three changes occurred during this time, which might have impacted 510(k) submission numbers.

The first change was publication of the Temple report in 1993, a review of the quality of clinical science submitted to CDRH in support of 510(k) submissions and PMA applications (FDA, 1993). The report was critical, observing (albeit on the basis of a small sample of PMA applications and

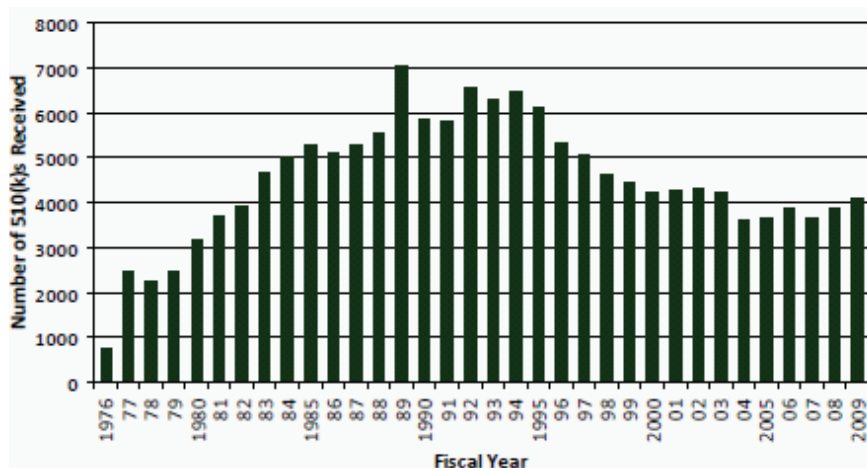


FIGURE 6-1 Original 510(k) submissions to CDRH, FY 1976–2009.
SOURCE: FDA, 2010a.

510(k) submissions containing clinical data) that studies submitted in support often failed to meet fundamental scientific standards. In response, the FDA initiated recruitment of additional scientists, including physicians and scientists, to perform premarket review of devices. While the review standard for 510(k) submissions was unchanged (that is, substantial equivalence), the review determinations began to shift from a descriptive to a data-driven base. The second change was issuance of FDA's final guidance, in January 1997, advising industry as to when modifications to a cleared device could be made without submitting a new 510(k) notification (FDA, 1997).¹ This guidance gave manufacturers autonomy in making decisions about devices with changes that were sufficiently minor as to preclude the need for premarket review. Finally, passage of the FDA Modernization Act in 1997 resulted in exemption of most Class I and many Class II devices from premarket review.² This Act resulted in decreased numbers of low-risk and, in some cases, moderate-risk devices subject to premarket review.

Those changes in administration, regulation, and statute might have had an effect on the volume of 510(k) submissions. The committee was unable to draw conclusions, however, on the basis of the available data as to whether innovation was influenced in any way by these changes.

¹Updated guidance was issued by the FDA on July 27, 2011, after the committee had completed its work.

²Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

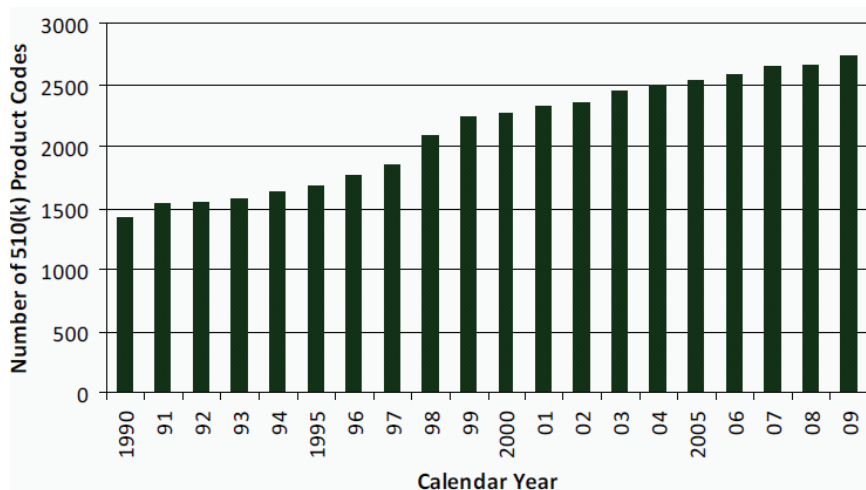


FIGURE 6-2 Number of 510(k) product codes, 1990–2009.
SOURCE: FDA, 2010a.

The number of types of medical devices also has grown. The FDA uses product codes to identify generic categories of devices. The product codes are organized by 16 medical specialties (for example, cardiovascular, general and plastic surgery, and orthopedic), and the medical specialties are listed in the *Code of Federal Regulations*.³ From 1990 to 2009, more than 1,000 product codes were added (see Figure 6-2).

In addition to the increase in 510(k) submissions to CDRH and the greater variety of types of products that CDRH must review, submissions have become longer and more detailed. As shown in Figure 6-3, the average number of pages per 510(k) submission in 2008 was more than seven times the number in 1983. In 2008, CDRH staff reviewed nearly 1.4 million pages of 510(k) submissions. Reasons for the increase in the length of 510(k) submissions are not readily apparent. The committee was not able to determine how often some types of data (for example, clinical data, bench-testing data, software-validation data, and labeling-comprehension studies) are included in 510(k) submissions, nor was it able to review a representative sample of complete (that is, not redacted) 510(k) submissions.

The technologic complexity of medical devices has increased substantially over the past 35 years as well. A 2010 FDA report states that “devices are unique among medical products in that they are defined by innovation, either through incremental evolution or disruptive revolution”

³21 CFR §§ 862–892.

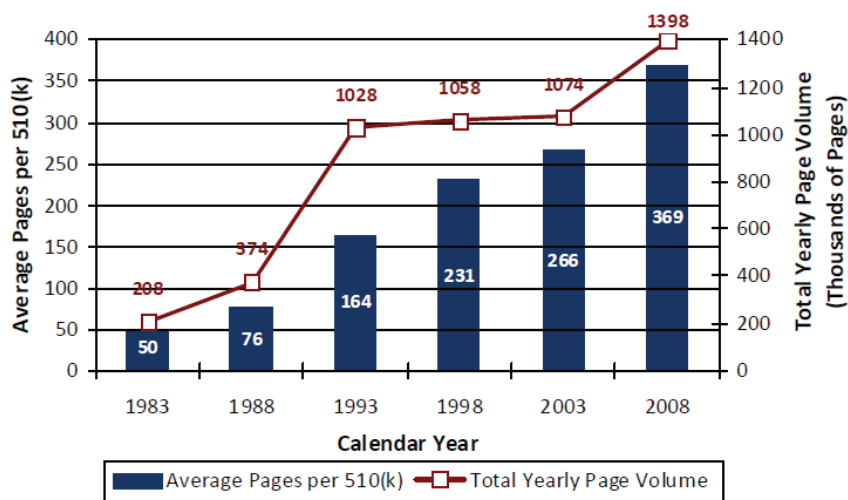


FIGURE 6-3 Pages per 510(k) submission and total page volume received, 1983–2008. SOURCE: FDA, 2010a.

(FDA, 2010b). Examples of new technologies in medical devices are software (incorporated in medical devices and as stand-alone medical devices), nanotechnology, and medical robotics. The evolution (and revolution) of science and technology creates many challenges related to the regulation of medical devices.

As medical devices become more complex, so do 510(k) submissions. As a result of the complexity and the increasing number and size of 510(k) submissions received each year, the burden on CDRH review staff is increasing (see Chapter 3). The growing complexity of medical devices also affects how the medical-device industry approaches the 510(k) clearance process. For example, industry representatives have indicated that they view the increased length of 510(k) submissions as a response to the lack of predictability in decision-making by CDRH. To avoid delays in clearance of their products, industry includes more information in the submissions than it might have in the past.⁴

Multiple Predicates and Split Predicates

As detailed in Chapters 3 and 4, predicates are used in the 510(k) clearance process as the basis for demonstrating substantial equivalence. The increasing complexity of medical devices is reflected in how predicates

⁴FDA Docket Number FDA–2010–N–0054.

are selected and used. Applicants may submit more than one predicate for several reasons, including these:

- The applicant is not sure which predicate is the most appropriate.
- The submission is part of a bundled submission.
- The new device combines functions of more than one predicate device, so the applicant submits more than one predicate (termed multiple predicates) to demonstrate substantial equivalence of the new device.
- The new device has the same intended use as one predicate and the same technologic characteristics as another predicate (termed split predicates).⁵

Multiple predicates and, in some cases, split predicates are cited in more than half the 510(k) submissions (FDA, 2010a). In general, multiple and split predicates are used in 510(k) submissions for new devices that are more complex than the predicates. Using more predicates leads to longer CDRH review times (FDA, 2010a). It is not clear whether the increase in review time of devices that have multiple predicates is related to the number of predicates or to the increased complexity of the devices. It may be appropriate for multiple and split predicates to play a role in premarket review of Class II devices if the CDRH review team has the necessary expertise to ensure a high-quality review and if appropriate postmarket activities (for example, postmarketing surveillance) are used.

Combination Products

Combination products are therapeutic and diagnostic products that combine drugs, devices, and biologic products (FDA, 2008). As new technologies emerge and older technologies evolve, combination products are increasingly complex. Over the past decade, it has been increasingly common to enhance the performance of medical products by using multiple products together. For example, a genetic test that is a 510(k)-cleared or a premarket-approved (PMA) device may be used with a drug or biologic with the aim of identifying patients whose genetic characteristics place them at heightened risk for drug-related injuries, or a stent that is a medical device may be coated with a drug with the aim of reducing complications associated with the stent or altering the underlying pathologic condition for which the stent was placed. Combined uses of medical products present complex regulatory issues because the resulting treatment or diagnostic test

⁵In January 2011, CDRH announced that it no longer intends to use the term *split predicate*. It plans to issue guidance to clarify the circumstances under which it is appropriate to use multiple predicates to demonstrate substantial equivalence (FDA, 2011a).

incorporates multiple components that cut across the traditional categories of FDA regulation—drug, device, and biologic.

In response to a growing trend toward combined uses of medical products, Congress called for the FDA to establish an Office of Combination Products (OCP) in the Medical Device User Fee and Modernization Act of 2002. *Combination product* is a term of art that has a specific meaning.⁶ To qualify as a combination product, the two (or more) constituent products need to be integrally combined or mixed with one another, packaged together in a single package as a unit, or, if packaged separately and in the particular circumstance of being used in combination, cross-labeled in a way that makes it clear that one is specifically intended for use with another product that is “individually specified” in the labeling. By that definition, the mere fact that products happen to be used together in clinical practice does not necessarily make them combination products for purposes of the FDA’s regulations. If products are simply used together in practice without constituting a combination product, each product retains its separate identity and is regulated separately. For example, a drug would be regulated as a drug and a device as a 510(k)-cleared or PMA-approved device. However, even in that circumstance, OCP may play a role in the clearance or approval process for the device, as is discussed in more detail later in this section.

When a pair or set of products does meet the definition of a combination product, special regulatory provisions apply. The aim is to reconcile conflicts that would otherwise make it difficult to comply with drug, device, and biologic regulations. On the basis of the combination’s primary mode of activity—that is, whether the combination achieves its medical purpose primarily through the action of the drug, the biologic, or the device—primary responsibility for premarket review is assigned to one of the FDA’s centers—the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, or CDRH. The responsible center, while having primary jurisdiction over the combination, will work closely with the other centers to ensure appropriate oversight of issues related to the combinations of other components. Because postmarket regulatory requirements also differ for drugs, biologics, and devices, OCP in 2008 prepared a proposed rule on postmarketing safety reporting for combination products (FDA, 2008).⁷ A final rule has not been published as of May 2011.

Information for FY 2008 indicate that a large percentage of combination products involve 510(k)-cleared devices. There were 330 original applications related to combination products. Of those, 120 were original 510(k) submissions, 2 were original PMA applications, 14 were original new drug applications, and 4 were original biologic license applications. The remainder

⁶21 CFR § 3.2(e).

⁷74 Fed. Reg., 50,744 (October 1, 2009).

consisted of 158 applications for investigational new drug status and 32 for investigational device exemptions (FDA, 2008). Thus, many combination products enter the market on the basis of having the primary mode of activity of the incorporated 510(k)-cleared device.

OCP also has a role in situations in which such products as medical devices and drugs are used in concert but not as true combination products. OCP may act as a convener and facilitator in developing guidance documents. Guidance documents can influence the regulatory review of medical devices. For example, imaging tests use devices, such as magnetic resonance imaging (MRI) and computed axial tomography machines; they may use contrast agents, such as gadolinium and iodinated contrast agents that are regulated as drugs; and they may use software, which is regulated as a device, for the reconstruction and processing of the resulting data. Guidance coordinated through OCP has influenced the review of software devices on the basis of perceived limitations imposed by the specific language that describes the indications for use of the contrast agents (FDA, 2009a). For example, the use of MRI contrast agents that are approved for use in imaging of the abdomen, but not specifically imaging of the liver or kidneys, might limit the ability of CDRH to review a software tool that analyzes data produced by approved MRI machines after administration of the MRI contrast agents if the data analyzed pertain to the liver or kidneys. Guidance documents may stymie innovation in software tools that would be used merely to analyze data that are being acquired daily in a clinical setting. Because the contrast agent is readily available for use in clinical practice, there is no practical mechanism whereby the software company can influence the supplier of the contrast agent to apply for expanded or specific new label indications.

Finally, the acceleration of device evolution is leading to increasingly novel devices that could not have been conceived of when the 1976 Medical Device Amendments and later amendments were written and enacted. For example, nanodevices include particles that are activated by biologic and pathologic processes, and some of them depend on metabolic pathways for the mechanism of action. Atomic and molecular computational platforms are under development. Complete “laboratories on a chip” are being delivered and used *in vivo*. Even previously contemplated combination products, such as drug-eluting stents, have evolved in ways that stretch the capabilities of the current system.

Some novel device–drug–biologic products—not truly combination products—are not well managed on the basis of the current combination-product concept. For example, nanoparticle drug-delivery systems (combination products of a drug or biologic encapsulated in a device) could be activated by external ultrasonographic energy (delivered by a device) and monitored by software analysis of resulting real-time images (a device).

Other than arbitrary assignment, there is no obvious lead agency for the review and approval of such a multipart product; in fact, the review might best be accomplished by multiple centers and branches.

Finding 6-1 Medical-device technologies have evolved rapidly and devices have become increasingly complex since the 1976 Medical Device Amendments.

Software

Software is used in medical devices, as medical devices (for example, medical-device data systems), and as a tool in producing medical devices. Manufacturers are increasingly using software in their medical devices. An analysis by Fu showed that a milestone was reached in 2006: since then, more than half the medical devices on the market have relied on software in some way (IOM, 2011). Software offers many benefits over hardware in some situations, for example, flexibility, ease of change, and usability in other applications. To reduce costs, many software vendors produce “software product lines,” that is, software designed to allow ease of variation to accommodate similar, and perhaps tailored, product lines. In some cases, general-purpose, off-the-shelf (OTS) software is incorporated directly into medical devices. The FDA’s software validation guidance addresses that situation, noting that “the use of off-the-shelf software in automated medical devices and in automated manufacturing and quality system operations is increasing” (FDA, 2002).

Software Is Responsible for an Increasing Number of Recalls

As software becomes more common in medical devices, it also is increasingly responsible for device failures and recalls. For example, CDRH (FDA, 2002) notes that

the FDA’s analysis of 3140 medical device recalls conducted between 1992 and 1998 reveals that 242 of them (7.7%) are attributable to software failures. Of those software related recalls, 192 (or 79%) were caused by software defects that were introduced when changes were made to the software after its initial production and distribution.

Fu noted that from 1999 to 2005, 11.3% of recalls were attributed to software, and 49% of recalled devices relied on software in some way (IOM, 2011). In the period 2002–2010, at least 537 recalls of software-based devices affected at least 1,527,311 devices. However, because of the limitations of recall data discussed in Chapter 5, there is insufficient information to determine the underlying issues in the increased rates. Because there is no

Arrhythmia Logbook Report						
Episode Query Selections						
Show All Episodes						
Episode	Date/Time	Type	Rate bpm		Therapy/ Duration	
			Zone			
1,230	23-JUN-05 19:10	Spont	VF	222	Diverted	
1,229	20-JUN-05 12:08	Spont	VF	216	Diverted	
1,228	21-MAY-07 21:22	ATR		130	?:?:??	
1,227	21-MAY-07 15:01	ATR		121	06:20 h:m	
1,226	21-MAY-07 15:01	ATR		119	00:45 m:s	
1,225	21-MAY-07 15:00	ATR		120	00:11 m:s	
1,224	21-MAY-07 15:00	ATR		119	00:16 m:s	
1,223	21-MAY-07 15:00	ATR		118	00:07 m:s	
1,222	21-MAY-07 14:59	ATR		119	00:09 m:s	

FIGURE 6-4 Example of a medical-device software malfunction.

SOURCE: Reprinted with permission from Halperin et al., 2008. © 2008 IEEE.

way to know the number of devices on the market or how many of them use software, it is not possible to know whether the change is related to the increasing proportion of software in medical devices or whether it is a signal of new or different types of problems and vulnerabilities in medical-device software.

A drawback of software is that it can be difficult to recognize problems, find their source, and fix them without adverse consequences. When software is used in medical devices, at least three outcomes are to be avoided:

- Unreliable and unavailable devices.⁸
- Insecure devices.
- Unpredictable behavior.⁹

Figure 6-4 is an example of how a software failure can be manifested. Here, the arrhythmia log is read from the bottom up. The episodes are in

⁸Reliability means that a system works as expected almost all the time; it rarely fails. Availability means that the system works whenever it is needed to work. There is no delay, and it is usable on demand.

⁹A device has unpredictable behavior if, for the same inputs, it gives different answers at different times.

BOX 6-1**Example Recall Announcement**

URGENT: Medtronic Announces Nationwide, Voluntary Recall of Model 8870 Software Application Card

MINNEAPOLIS, Sept. 22, 2004 - Medtronic, Inc. (NYSE: MDT) today announced a voluntary recall that involves all Version AAA 02 Model 8870 software application cards in the U.S. that are used in conjunction with all Model 8840 N'Vision™ Clinician Programmers. This action has been classified by the Food and Drug Administration (FDA) as a Class I Recall. . . . a reasonable probability that the use of or exposure to the product will cause serious adverse health consequences or death.

Medtronic became aware in August 2003 that some users had mistakenly entered a periodic bolus interval into the **minutes** field, rather than the **hours** field, potentially resulting in drug overdoses. Data entry errors have been related to seven serious injuries and two deaths. The previous model 8870 software application card did not provide a label for the hours/minutes/seconds fields; the new software has this labeling.

SOURCE: FDA, 2009b.

chronologic order, and they inexplicably and suddenly move from 2007 back to 2005. Such an error can occur only when software is faulty.

Similar software failures are noted frequently in recall announcements. For example, Medtronic issued a press release related to the Class I medical-device recall of the Medtronic 8870 Software Application Card Version AAA 02 (see Box 6-1).

The *Guidance for Premarket Submissions for Software Contained in Medical Devices* for industry and FDA staff issued on May 11, 2005, poses questions about problems with OTS medical-device software (FDA, 2005a):

What is it about “network-connected medical devices” that causes so much concern? . . . Vulnerabilities in cybersecurity may represent a risk to the safe and effective operation of networked medical devices using OTS software. Failure to properly address these vulnerabilities could result in an adverse effect on public health. A major concern with OTS software is the need for timely software patches to correct newly discovered vulnerabilities in the software.

The “vulnerabilities” are problems with the software that can be exploited by a malicious agent or can simply malfunction if the software is subjected to particular conditions. For instance, poorly designed software

may malfunction if it receives a type of input that it does not expect or if it conflicts with other devices that are communicating along the same channels. A patch is the application of a software correction; the resulting modified software should work as desired. However, the FDA's request for "timely patches" suggests that patching is straightforward. In the committee's opinion, it is not.

Beattie et al. (2002) analyzed the timing of patch availability and application. The researchers concluded, "Patch too soon, and you may suffer from instability induced by bugs in the patches. Patch too late, and you get hacked by attackers exploiting the vulnerability." And patches are not always available as soon as a problem is discovered. The second Tuesday of each month is known to Microsoft Corporation's customers as "patch Tuesday": the day on which patches are made available for application to existing systems. Only when a problem is considered an emergency is a patch offered off-cycle to customers.

Microsoft is not alone. For example, Oracle (2010) notes that "Oracle Sun releases over 4,500 patches every year, for Solaris 8, 9, and 10, SPARC and x86, Solaris Cluster, Middleware, Developer, Storage, and other products. Just 17 have been withdrawn after release in the last year due to serious issues."

Software Is Different from Hardware

Pfleeger et al. (2002) have written extensively on how software is different from hardware. The authors identify three key characteristics of software that make it different from hardware:

- Software developers are overoptimistic. Careful empirical studies have shown that software developers, particularly testers, often assume that they have found the last problem in the software under scrutiny. That is, they commonly stop looking once they find a problem, not recognizing that other problems remain. Their optimism results in overconfidence in both testing techniques and the degree to which the tests exercise all the functions implemented by the software. Such optimism is shared by hardware testers but seems to be extreme in software testers. Indeed, Beck (2004) noted that "optimism is an occupational hazard of programming, feedback is the treatment"; and Jorgensen (2010) has shown that, counterintuitively, identification of more risks can lead to developers' overconfidence and overoptimism.
- Software is discrete, not continuous. Unlike hardware, software is extremely sensitive to small errors. Off-by-one errors, negligible in hardware, can result in huge changes in software. Just as an off-by-

one telephone number can send a call around the world, an off-by-one software error can lead to potentially dangerous outcomes. And because software is discrete, interpolation is difficult and sometimes impossible. Whereas hardware that passes a test at two different values can be assumed to pass for all values in between (as with bearing a load, for instance), software must be tested for every possible class of values that it can handle. Finally, there are no safety margins in software akin to those in hardware; software developers cannot double the strength of a material. Instead, every possible adverse situation must be anticipated and designed for, and resilience takes the form of multiple systems that perform the same critical functions.

- Software is immature and subject to rapid change. The National Research Council Committee on Information Systems Trustworthiness notes that “because a typical Networked Information System is large and complex, few people are likely to have analyzed one, much less had an opportunity to study several. The result is a remarkably poor understanding today of design and engineering practices that foster NIS trustworthiness” (NRC, 1999).

For those reasons, software is substantially different from hardware and should be treated and tested by different means. In particular, there is more uncertainty in software test results than there would be in testing an equivalent hardware implementation. An implication of the difference is that hardware should not be considered a predicate for software.

Software Validation Requires Interpretation Within the System Context

The FDA provides guidance on how software can be validated to ensure that it is performing its functions correctly (FDA, 2002):

Software validation is a requirement of the Quality System regulation, which was published in the Federal Register on October 7, 1996 and took effect on June 1, 1997.¹⁰ Validation requirements apply to software used as components in medical devices, to software that is itself a medical device, and to software used in production of the device or in implementation of the device manufacturer's quality system. . . . FDA considers software validation to be “confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.”

¹⁰61 Fed. Reg., 52,602; 21 CFR pt. 820.

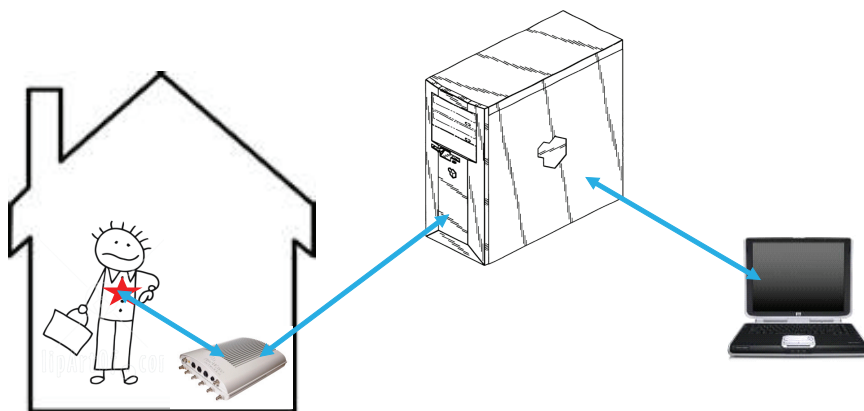


FIGURE 6-5 Transmission of medical data.
SOURCE: Adapted from Figure A, Halperin et al., 2008.

In other words, the FDA requires objective evidence that demonstrates predictability and consistency of function. To provide that evidence, a medical device must be viewed as part of a larger system in which it functions. Figure 6-5 illustrates what that larger system might contain. In the figure, the patient has a medical device that transmits data to a receiver in his home. In turn, the data are sent to a server that eventually places the data on a physician's laptop. The communication may work in two directions; after the physician evaluates the patient data, she may transmit signals to change the settings in the medical device, for instance, changing dose amount or frequency.

It is essential that the “system boundary” be defined to include all devices and situations that may interact with each other. To see why, consider the findings of Lee et al. (2008). The researchers examined an MP3 player to see whether there were interactions with pacemakers and implantable defibrillators. Although no serious electromagnetic interference by the MP3 player was found, there were other irregularities:

- Device interference by headphones (not the player itself) was documented in 14 of 60 (23%) patients.
- Inappropriate (asynchronous) pacing was observed in 4 of 27 (15%) pacemaker patients.
- Inhibition of implantable cardioverter defibrillator detection occurred in 10 of 33 (30%) patients who had those devices.

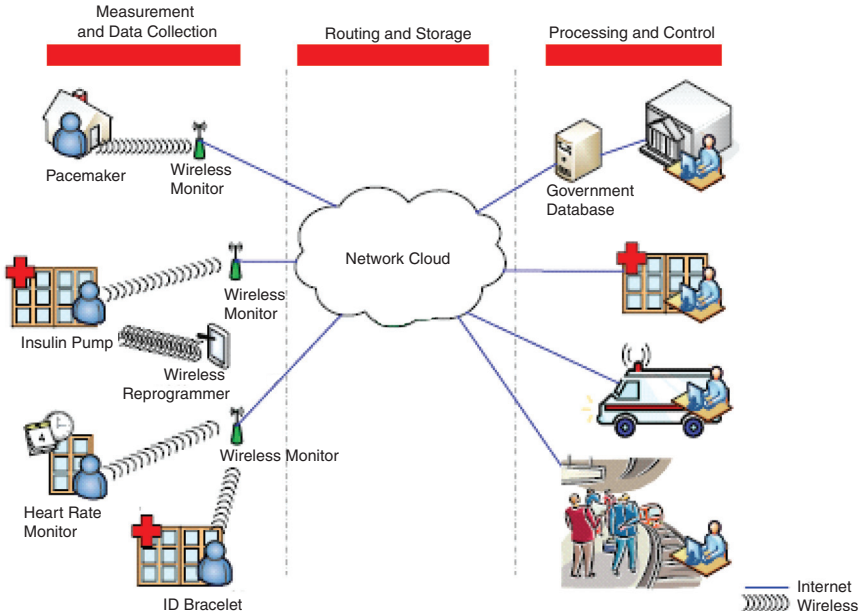


FIGURE 6-6 Vision of future data transmission.

SOURCE: Adapted from Figure 1, Defend et al., 2008. Reprinted with permission.

The researchers concluded that clinically significant electromagnetic interference could occur when headphones were placed close to implanted pacemakers and implantable defibrillators.

Figure 6-6 illustrates a vision of medical-device interaction in the not-so-distant future. Devices will be collecting, analyzing, storing, and transmitting data in many ways to large numbers of people, institutions, and other devices. It is essential that software validation take all those system elements into account in an effort to anticipate interactions among the elements that may at least add to uncertainty and at worst cause patient harm.

Software Validation Evidence Should Be Organized as an Assurance Case

The differences between hardware and software mean, among other things, that software can never be tested completely. As a consequence, ensuring the safety of software in a medical device requires presenting a convincing argument that the actions taken, when viewed collectively, support the claim that the device is likely to be safe. Similar arguments are made in other disciplines, such as nuclear power-plant safety, in which a “safety

case” is presented by the developers and reviewed by a body of experts who determine the argument’s soundness.

The case usually has three parts:

- One or more claims that some set of properties is satisfied.
- A body of evidence (from a variety of sources) supporting the claims.
- A set of arguments that link the claims to the evidence.

However, software developers and device manufacturers often focus too much on producing evidence and too little on building the associated arguments, analyzing their soundness, and accounting for uncertainty (Pfleeger, 2005). Schum (1994) identified four distinct categories of evidence, some with more uncertainty than others: tangible, testimonial, accepted facts, and missing evidence. Each has an associated degree of credibility, depending not only on its type but also on its source and its sensitivity to error.

To address soundness, several key questions can be asked:

- What kinds of evidence (and how much evidence) are needed to demonstrate that a device works? Some technologies show their effects even before the software is fielded, but some (such as those affecting reliability) can be evaluated only after a system is in use. Evidence must demonstrate the effects, both before and after. The evidence must also enable comparison of outcomes when the technology is used and when it is not used.
- Who provides the evidence, and who vets it? Many vendors provide evidence of their products’ effectiveness; many are eager to demonstrate that their new tools can make a favorable difference to developers or users. But that enthusiasm can bias the results even when vendors take great pains to eliminate it. Independent assessment is almost always preferable.
- If a technology works in one domain, what does that say about how it works in other domains? Evidence gathered in one context or environment might or might not apply to others.

Rather than be dismayed by the nature and variability of the uncertainty of evidence, one can use the uncertainty to advantage. Evidential force is the degree to which each piece of evidence contributes to or detracts from an argument that uses it. Ideally, each piece of evidence adds to an argument’s overall force.

Bloomfield and Littlewood note that arguments involving diversity of evidence are stronger than arguments involving multiple replications of the same kind of evidence. Their work is motivated by the need for strong evidence in making decisions about safety-critical systems. The “multilegged

argument,” in which each leg handles a different type of evidence, can be easier to analyze than one comprehensive argument. Moreover, the legs need not be independent. The extra legs usually provide more confidence than one leg alone, but the extra cost of the extra confidence must be justified (Bloomfield and Littlewood, 2003).

Finding 6-2 Manufacturers are using increasing amounts of software in devices and as devices; the increase is expected to continue. Software offers many benefits over hardware, including flexibility, ease of change, and the possibility of use in other devices.

Finding 6-3 Software is responsible for an increasing number of recalls. There are insufficient data, however, to determine whether the increase reflects the increasing proportion of software in medical devices or a new and different set of problems and vulnerabilities.

Finding 6-4 Software is different from hardware and therefore requires a different kind of evaluation.

INNOVATION AND THE 510(K) CLEARANCE PROCESS

In considering the role or impact of the 510(k) clearance process on innovation, it is first necessary to define innovation. It has been defined as “the introduction of something new,” “a new idea, method, or device,” or “a new method, idea, product, etc.” (Merriam Webster, 2011; Oxford Dictionaries, 2011). Doris Estelle Long offers this regarding innovation: “It has been defined as everything from ‘introducing something new’ to ‘a scientific approach for finding newer better ideas and solutions to problems, which make life easier and simpler to live’” (Long, 2008). Long went on to quote Joseph Schumpeter’s definition of innovation as “the introduction of a new good . . . a new method of production . . . the opening of a new market . . . the conquest of a new source of supply . . . [and] the carrying out of the new organisation of any industry.” Everett Rogers, author of *Diffusion of Innovations*, defines innovation as “an idea, practice, or object that is perceived as new by an individual or other unit of adoption” (Rogers, 2003). Susan Bartlett Foote in her book *Managing the Medical Arms Race: Public Policy and Medical Device Innovation* cites several variations, including “certain technical knowledge about how to do things better than the existing state of the art” (Teece, 1986) as cited in (Foote, 2005). Ahn et al. (2009) discussed the criteria for the adoption of new technology by posing the following question: “Can this technology improve clinical care for my patients?”

Scott Berkun, author of *The Myths of Innovation*, cited one definition of innovation in his book as “significant positive change” but went on to sug-

gest how such a relatively simple definition “burdens creators to understand the recipients’ perspective of whatever they make” (Berkun, 2010). That is, what may have been intended as a favorable change by an innovator may not be similarly perceived as favorable by the recipient of such an innovation, and thus simply associating innovation with a perception of positivity may not be sufficient. Berkun suggests resisting overuse of the word as a stand-in for a more specific description: rather than state something as innovative, describe its benefits in more precise detail. For considering the utility, practicality, or overall goodness of innovation, Berkun offers the following criteria: an innovation can be good for you, good for others, good for industry or economy, good for a society, good for the world, and good for all time.

Although those general definitions may be technically accurate, they lack the nuance of the term as it is related to technology and the medical-device industry. Innovation is broadly viewed as describing new favorable changes, but more precise definitions of innovation may indeed require the consideration of the context in which it is being discussed. In the context of medical-device regulation, it is reasonable to use patient care and utility as a test for innovation. Foote discusses innovation in the context of medical devices and says that it “embraces the frontiers of science and engineering, adapting computer technology, nanotechnology, and biotechnology to medical applications. Many of these technologies are delivered by physicians in in-patient and out-patient settings and are embedded in the service delivery system. Physicians’ needs and experiences in clinical settings often trigger innovation and incremental improvements; physicians also require ongoing training to effectively use innovative therapies” (Foote, 2005).

Although a specific definition of innovation from the FDA was not evident, the FDA does discuss innovation in various ways. For instance, the FDA defines its charge on its Web site under the banner “What We Do.” Here, the FDA defines its role in terms of innovation as follows: “FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health” (FDA, 2010d). It is assumed that the use of the word “medicines” in this context does not exclude devices. In the context of devices, a whitepaper from CDRH in February 2011 titled *CDRH Innovation Initiative* states that “new scientific discoveries or novel ideas are often at the root of innovative medical device development—whether the product is a transformative technology, a modified version of an already marketed model, or a novel application of existing tools or scientific approaches” (FDA, 2011b). Those statements suggest that the FDA considers an attention to innovation to be at the heart of its overall mission and, more specifically, that CDRH consid-

ers innovation to encompass new ideas that lead to both incremental and sweeping changes in technology.

Process of Innovation

An assessment of innovation produces not only a number of definitions but also various strategies, processes, and principles. Innovation is found to exist not in isolation but as part of a larger structure of both thinking and doing. Berkun discusses the process of innovation and how it is often incorrectly paired with the term *epiphany* and how most innovative advances were *not* the product of any singular epiphany but “a combination of things that existed before. . . . For most, there is no singular magic moment; instead, there are many smaller insights accumulated over time. . . . It’s simply the final piece of a complex puzzle falling into place” (Berkun, 2010, xvii and 6-9). Foote also offers that innovation is “process leading to technical change” (Foote, 2005). The author goes on to describe innovation as consisting of two stages; stage 1, discovery, which encompasses science, invention, and development; and stage 2, distribution, which encompasses adoption and distribution. Foote goes on to suggest that the progression of innovation cannot exist without each element in place; nor is it a purely linear process, but rather an iterative one. This last point was supported by Privitera et al. (2009) by examining the interconnectivity of basic-science research and product development in designing medical devices when the appropriate design of a new device allows and facilitates the translation of a seemingly complex product into “easy-to-use, innovative products.”

In April 2009, *The Lancet* published a three-part series summarizing a study of surgical innovations that provided an overview of how the innovations initially occur and are eventually adopted (Barkun et al., 2009; Ergina et al., 2009; McCulloch et al., 2009). This model, termed the IDEAL model, divided the process into five stages: innovation (or idea), development, exploration, assessment, and long-term study. Stage 1, innovation, was defined as “the first use of a new procedure in a patient, prompted by the need for a new solution to a clinical problem” (McCulloch et al., 2009). Linehan and Chaney (2010) similarly concluded that “clinical needs provide opportunities for medical device innovation” through identifying an unmet or undermet clinical need, harnessing new insight into the physiology of a disease or a new diagnostic approach, new developments in technology, or some combination of such factors.

In its 2004 report, updated in 2010, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, the FDA outlined a critical path for medical-product development from basic research to FDA approval (FDA, 2010c). In describing this critical path from scientific innovation to commercial product, the FDA identified three

distinct scientific and technical dimensions: (1) assessing safety for each stage of development, (2) demonstrating medical utility or, more simply, that the product benefits people, and (3) having an industrialization component that considers whether a product can go from concept or prototype to a manufacturable product (endorsing the concept that innovation is a process, not one defined event).

Given the above discussion, the committee made a few determinations about the concept of innovation in a general sense:

- There is no single accepted definition of innovation.
- Innovation most likely is a result of several factors that coalesce toward a single objective.
- Innovation often occurs in small increments rather than quantum leaps.
- Innovation is generally considered to be a change toward the greater good rather than the opposite.

The Committee's Working Definition of Innovation

It is with those ideas in mind that the committee agreed on a definition of innovation through which it would attempt to assess whether the current 510(k) clearance process optimally protects patients and promotes innovation in support of public health. The committee believes that given the broad interpretation of the term it should define innovation not simply as a change but as a favorable change in the context of public health. The committee also believes that given the complexity of the process of innovation and the iterative and combinatorial nature of the process, a broad definition would be more accurate than one that sought to create a list of specific attributes. In the context of this report, the committee defined innovation as improving the quality of, efficiency of, or access to health care. To revisit the charge given by the FDA to the committee, the question that needs to be answered is, Does the current 510(k) clearance process optimally protect patients and promote innovation in support of public health? Answering that question requires a general understanding of whether and how CDRH promotes innovation.

Does the 510(k) Clearance Process Facilitate or Inhibit Innovation?

In testimony to the US House Subcommittee on Health of the Committee on Energy and Commerce in February 2011, Jeffrey Shuren, director of CDRH, indicated that it was the role of the FDA to “ensure the safety and effectiveness of the medical products that Americans rely on every day, and also facilitate the scientific innovations that make these products safer,

more effective, and more affordable” (Shuren, 2011). In February 2011, CDRH launched the CDRH Medical Device Innovation Initiative, a multipronged program that proposes actions that CDRH could take to “help accelerate and reduce the cost of development and regulatory evaluation of innovative medical devices safely and based on sound science” (FDA, 2011b). Those actions include facilitating the development and regulatory evaluation of innovative devices through new priority review programs and a streamlining of the pre-existing *de novo* pathway, strengthening the US research infrastructure, and improving its preparedness for transformative innovative technologies and scientific breakthroughs. The FDA’s initiative explicitly outlines a strategy to promote innovation in CDRH, but what is less clear is whether the 510(k) process promotes innovation in support of public health. A cursory look at the original legislation and later changes, additions, and modifications may provide some insight.

The structure of the Medical Device Amendments of 1976 rejected premarket approval for all devices, limiting PMA to Class III devices. That approach balanced the adverse effects of preclearance on innovation with the public-health benefits of premarket review of products. For new products with a lower degree of risk, it would be sufficient to demonstrate that the products were already classified in a lower class and, for Class II devices, complied with performance standards. During the transition period and thereafter in showing that the device was already classified, market entry was based on substantial equivalence. The substantial-equivalence standard was vague and arguably required equivalence but precluded, or at least did not mandate, superiority. The Office of Technology Assessment commented on the concept of substantial equivalence as a tool for device clearance, stating that as devices “diverge more and more from their preamendment antecedents, it will be harder for manufacturers to use the substantial equivalence method of market entry” (OTA, 1984). It could be reasonably argued that allowing market entry on the basis of the equivalence of one device to a pre-existing device is not in support of innovation. Congress showed some concern during a House Subcommittee on Health hearing in 1987 that equivalence would freeze the world as it was, indicating that technologic improvements had continued to occur in the 10 years since the initial legislation but that under the concept of substantial equivalence “new devices need not incorporate these improvements: they need only be as safe and effective as similar devices on the market before 1976.”¹¹

In the late 1980s, the FDA redefined the term *substantially equivalent* and Congress endorsed this interpretation with the Safe Medical Devices

¹¹Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 336-47 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

Act of 1990 (SMDA) that allowed for devices to be substantially equivalent if they had different technologic characteristics from the predicate device but were “as safe and effective as a legally marketed device.” In so doing, it explicitly sought to promote evolution of the marketplace (new devices) toward improvements. The law, however, did not force innovation if it is defined as bringing about change for the greater good, in that the new definition of *substantial equivalence* still allowed manufacturers to use potentially inferior predicates as long as they had the same technologic characteristics as a predicate device.

As discussed in Chapter 2 and Appendix A, the Food and Drug Administration Modernization Act of 1997 had various implications for innovation in the FDA. With respect to Class II devices and the 510(k) process, the effect of the 1997 amendments on innovation were indirect, lessening regulatory burdens and limiting the scope of FDA preclearance requirements. Specific provisions that lessened regulatory burdens included the *de novo* process, which permitted devices determined *not* to be substantially equivalent to another device to be classified in Class I or Class II rather than going through the PMA process; the least burdensome rule, which specified that the FDA could request information only if it were necessary to make a determination of substantial equivalence (allowing the FDA to down-classify devices in light of postmarket controls); reaffirming the 90-day period for 510(k) reviews; and introducing priority reviews for important new devices. Finally, the various user-fee laws, beginning in 2002, were intended to ensure that the FDA had adequate resources to complete reviews within the statutory time limits, increasing predictability of review.

In reducing regulatory burdens and providing additional resources to allow for timely review, the changes in the original legislation over the past 35 years neither forced nor rewarded innovation. Although it may be argued that such changes may improve the likelihood of innovation, it remains unclear—and the committee argues that it is indeterminable, given current data—whether those changes promoted innovation in balance with public health rather than at its expense.

THE MEDICAL-DEVICE ECOSYSTEM

The medical-device ecosystem includes the environment that affects medical-device development, commercialization, and availability to consumers. The regulatory aspect of the ecosystem, including the 510(k) clearance process, is covered in detail in earlier chapters and is not repeated here.

Medical devices are developed by commercial interests that range from small startup companies to established conglomerates. Publicly traded US medical-device companies generated revenues of \$188.8 billion in 2008

(Ernst and Young, 2009). Most of the revenue from medical devices is earned by 30 companies (Kalorama Information, 2010).

Hundreds or thousands of companies operate in the medical-device market, and most of them are small: more than 80% have fewer than 50 employees (MDMA and NVCA, 2009). Startup companies, generally supported by investments made by venture capitalists and other investors, are viewed as the drivers of innovation in the medical-device industry (Platzer, 2006).

510(k) clearance or PMA often is cited as an event that triggers transactions that result in change in ownership of intellectual property and return of investment to venture capitalists and other investors. Larger companies often are willing to wait to acquire smaller companies or their intellectual property after 510(k) clearance or PMA approval even if they have to pay a premium.

Many startup medical-device companies generate little or no sales revenue during the development phase before they receive permission to commercialize a device, and the funds invested in such companies by venture capitalists and other investors must sustain the companies until regulatory approval or clearance. Another potential barrier to the economic viability of both small and large companies is supportive insurance for coverage, payment, and reimbursement. In general, for nearly all device-based therapies and many diagnostic tests, a device must be cleared or approved and have valid current procedural terminology codes for a medical service before an insurer or payer will consider covering the service.

Delays during any of those phases extends the “burn rate” of capital (that is, the amount of funds spent in a given period) and can create financial difficulties for companies, particularly startup companies, which often have limited financial resources. A positive return on invested capital is important for maintaining a robust environment for innovation of medical devices (Platzer, 2006). Investment return is affected by several factors, including the state of the economy, changes in patent law, and challenges in getting medical devices through regulatory and reimbursement pathways (MDMA and NVCA, 2009). According to company representatives, the medical-device development environment is “fragile and extremely sensitive” to changes in the cost of innovation (IOM, 2010). Because achieving access in the market is critical in defining investment return, any delay in the ability to commercialize can have serious consequences, not only to specific devices and device companies but to the entire medical-device ecosystem.

The vast majority of medical devices subject to FDA premarket review—more than 90%—are brought to market via the 510(k) clearance process. The FDA receives about 4,000 510(k) submissions each year (FDA, 2010a). Because the 510(k) pathway is less expensive and less time-consuming than the PMA pathway, medical-device companies view it as a useful mechanism

for bringing moderate-risk devices to market. Representatives of medical-device companies have indicated that in recent years it has been increasingly difficult to move devices through the 510(k) pathway (Ernst and Young, 2009; IOM, 2010, 2011; Makower et al., 2010; MDMA and NVCA, 2009). Medical-device industry representatives believe that overall the 510(k) clearance process works well but that there is increasingly a lack of predictability and transparency in CDRH (IOM, 2010; Makower et al., 2010). They have voiced concern that those factors have led to increased time to 510(k) clearance of products, which has created an unfavorable environment for development of medical devices. Additional time to 510(k) clearance has the potential to affect a large number of medical-device companies and, by extension, medical-device innovation. Other industry concerns related to the 510(k) process include inadequate communication with CDRH staff, lack of publicly available information about predicate devices (needed to demonstrate substantial equivalence), issues surrounding the *de novo* process, and issues surrounding the use of standards and other types of evidence to show safety and effectiveness in the absence of a predicate device.

Reports from the venture-capital community have indicated that funding availability for device development has been adversely affected, in part by the regulatory environment and economic circumstances (IOM, 2010; Makower et al., 2010). However, the fiscal environment is more favorable once a device has achieved regulatory permission for commercialization and favorable coverage, payment, and reimbursement policies than before that benchmark in the device life cycle is achieved. As previously stated, a company that benefits from that more favorable economic environment is often a different company from the one that must contend with the development of the device, including premarket regulatory clearance or approval.

One of the critical economic pressures in the device ecosystem is obtaining favorable coverage, payment, and reimbursement policy decisions from payers, such as the Centers for Medicare and Medicaid Services (which manages the Medicare and Medicaid programs) and private health insurers. With rare exception, however, payers do not contribute to the collection of clinical data (for example, by funding clinical care during clinical trials) that could be used in making reimbursement decisions. One of the notable exceptions is the Medicare Coverage with Evidence Development program, which includes several examples of data collection for diagnostic and therapeutic devices as used in the course of clinical care.

As Feigal and others have opined, the medical-device life cycle includes not only premarket evaluation but continued postmarket evaluation, which might lead to the development of new devices or improvements in marketed devices (IOM, 2010). (Postmarketing surveillance is discussed in more depth in Chapter 5.) High-quality postmarketing surveillance data are useful for several parties. In addition to industry use of the data to support future

device development and improvement, regulatory agencies could use them to track how devices are used in clinical settings (for example, compared with labeled intended use)¹² and how devices function (for example, identifying adverse events and effectiveness); healthcare providers increasingly need them for the Maintenance of Certification process as mandated by the American Board of Medical Specialties; institutional providers need them for quality-review assessments; patients and patient-advocacy organizations could use them to assist in educational efforts; and professional organizations could use them to assess their members' needs (for example, educational and strategic planning needs).

Industry has several potential partners in the ecosystem for collection of postmarket information. And the clinical environment in which devices are used is quite varied, ranging from increasingly high-technology inpatient to underdeveloped outpatient sites of service. However, new and evolving tools could be used in varied clinical environments to conduct postmarketing surveillance. Professional societies could establish registries by using information extracted from electronic medical registries in the high-technology inpatient setting, and mobile computing devices, such as "smart phones," facilitated by the availability of Unique Device Identification codes, might have utility in collecting and transmitting data in many outpatient settings. Developing and understanding a holistic view of the device ecosystem could contribute substantially to improving various aspects of it, including the regulatory mechanisms.

Finding 6-5 Industry-funded assessments of the effects of the 510(k) clearance process report that implementation of the process leads to a lack of predictability and transparency, which in turn has an adverse effect on venture-capital investment.

Finding 6-6 The committee did not find assessments of how much and in which way innovation is influenced by the 510(k) clearance process.

Finding 6-7 There is little collaboration in collection of postmarketing surveillance data among the FDA, healthcare facilities, healthcare providers, the medical-device industry, professional societies, payers, and patient-advocacy groups.

¹²For example, incorporation of an off-the-shelf product, such as a smart phone or commercial software application, might stretch proposed use beyond intended use and require evaluation of the technology by the FDA.

GLOBALIZATION OF THE MEDICAL-DEVICE INDUSTRY

The United States is the largest consumer and producer of medical devices, with about half the world's market. The European Union (EU), Japan, Canada, and Australia also have large, stable medical-device markets, and the developing world is rapidly increasing both its consumption and its production of medical devices. In addition, medical-device manufacturers are increasingly multinational—some companies based in one country produce the majority of their devices in another (ITA, 2010). Of the top 10 medical-device manufacturers, 7 are American and 3 are European. The market share in the Indian subcontinent and China is increasing rapidly. The global market for medical devices was \$290 billion in 2009 and is expected to be \$312 billion in 2011 (Kalorama Information, 2010). Studies sponsored by industry have suggested that premarket review times for medical devices, particularly more complex devices, are longer in the United States than in the EU and that some companies have shifted toward obtaining approval for their devices in the EU first (Davis et al., 2011; Makower et al., 2010). A study of comparable recall data from the United States and the EU found similar recall rates in the two. The study authors concluded that the EU's approval process and shorter time to market for medical devices did not affect patient safety adversely (Davis et al., 2011).

Foreign establishments exporting medical devices to the United States must register with the FDA (FDA, 2009c). Medium-risk and high-risk imported devices must be cleared or approved for marketing by the same standards and by the same processes as equivalent US-made devices. Low-risk imported devices do not require premarket review, only registration and listing and, as appropriate, conformity with other regulations, such as quality-system regulations and labeling requirements.

Medical-device regulations in the United States were developed largely at a time when the medical-device industry was primarily domestic, but now medical devices are global products in a global market. Medical-device companies are increasingly multinational. In this environment, regulators and consumers can reasonably assume that any given device may have been manufactured in a jurisdiction different from the one in which it is being used. Device components may also be made in several countries. To bring a medical device to market in multiple jurisdictions, manufacturers must navigate the regulatory environments of each jurisdiction. Additional time to market and costs occur if the jurisdictions' regulatory frameworks differ substantially. Given the multinational nature of the market, the committee found it instructive to examine the international environment of medical-device regulations when considering its charge.

The FDA and medical-device manufacturers operate in the wider context of international markets and regulatory structures. All developed nations have some regulatory frameworks in place to ensure medical-device

safety and effectiveness. Recognizing the multinational environment of medical devices, governments and industry joined to form the Global Harmonization Task Force (GHTF) to attempt to harmonize regulation across borders. The GHTF (discussed below) has issued many guidance documents and promoted a pilot program for harmonized regulatory approval. Several countries, including Japan and India, are moving toward using the GHTF principles, although there has yet to be a large-scale movement toward standardization among regulators or industry (IOM, 2010).

International Approaches to Medical-Device Regulation

In examining other systems, the committee focused on the EU as the nearest counterpart of the United States in the structure and scope of the market. However, it is important to note key differences between the two. First, although the EU acts as a single entity with respect to trade, it is made up of 27 member states, 16 of which use a common currency. Member states are obliged by treaty to conform to communitywide laws and regulations but retain sovereignty over their own territories. Second, the US system has been in place much longer than the EU system. Although some member states of the EU, most notably the United Kingdom, had long regulated medical devices, most had not. Thus, the FDA has greater experience than most countries in regulating medical devices. Beginning with a clean slate, however, gave the EU the opportunity to put into place a logic model that used the latest thinking in risk analysis. In the United States, the standard for clearance is substantial equivalence to a previously cleared device; but the EU and other countries that tightly regulate medical devices do not rely on this standard. Finally, the primary role of the EU is to promote trade among its members and between Europe and the rest of the world.

Unlike the United States, the EU has different governmental structures for the regulation of medical devices and of pharmaceuticals. Pharmaceuticals are overseen by a centralized authority, the European Medicines Agency. Medical devices are regulated by the Directorate General for Health and Consumers, which is responsible for a wide variety of consumer products. The legislation governing medical devices is written as a directive. Member states are bound by treaty to enact directives by transposing them into national law, but governments are given some latitude as to the details of the law as long as the intended effect is as laid out in a directive. The directives are in contrast with regulations, which have the effect of becoming law throughout the European Community as written immediately on adoption by the European Commission. Regulations have been used to cover pharmaceuticals but have not been used for medical devices. In the case of directives, it is the national law that is binding, not the directives themselves. That

approach leads to some variation among member states, particularly in enforcement procedures and the imposition of sanctions (Grubb et al., 2011).

The Directives

Three European Commission directives govern the regulation of medical devices:

- Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD).
- Council Directive 93/42/EEC on Medical Devices (MDD).
- Council Directive 98/79/EC on in Vitro Diagnostic Medical Devices (IVDD).

The directives lay out the goals, structure, and standards for both safety and marketing. They are closely tied to one another in content and structure, but they differ in their requirements according to the category of device. As noted earlier, before the passage of the directives (in 1990, 1993, and 1998, respectively), medical devices in the EU were regulated at the national level if at all (Grubb et al., 2011). The impetus for the change was the so-called new approach of 1985 that aimed to standardize the technical requirements for a wide array of products. Its goal was to remove barriers in the internal market caused by differing regulatory standards among the member states. The AIMDD, issued in 1990, was the first directive concerning the regulation of medical devices in the EU. Among its objectives were that “active implantable medical devices must give patients, users and other persons a high level of protection and achieve the intended level of performance when implanted in human beings” and that “national provisions ensuring that safety level should be harmonized in order to guarantee the free movement of active implantable medical devices without lowering existing and justified levels of safety in the Member States” (European Commission, 2001). Patient safety and confidence were seen as necessary components of the free movement of goods within the internal market and thus important to the promotion of free trade. In 1993, the AIMDD was amended by the MDD, which covered a broader spectrum of products. The MDD also laid out the risk-classification structure that would be used in the approval process. Finally, in 1998, the council issued the IVDD, a directive covering in vitro devices and based largely on the two earlier directives.

The directives have been amended several times since their adoption to reflect changes in technology and in response to issues that have arisen over the course of implementation. In 2008, the European Commission started the process of a major revision of the entire medical-devices framework, known as the Recast of the Medical Devices Directives. The recast

began with a public consultation of stakeholders in 2008 and has continued through consultation with the European Commission's Medical Devices Experts Group and a further public consultation concerning *in vitro* devices in 2010 (European Commission, 2010b). Among the changes under consideration are consolidating the three main medical-device directives and five supporting directives into one piece of legislation, tightening oversight and accreditation of notified bodies (described below), and creating an EU-level entity in line with that which exists for pharmaceuticals to oversee the regulation of medical devices. It is unclear which changes will be adopted by the European Commission. According to the Roadmap 2011 posted on the European Commission's Consumer Affairs Web site, adoption of the initiative is expected in the first quarter of 2012 (European Commission, 2010d).

In the directives, a medical device is defined as

any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

In 2007, Directive 2007/47/EC made extensive amendments to the MDD, including the addition of software to the definition of a medical device and making software validation part of the essential requirements that had to be met to establish conformity with safety standards.

A device must perform its "intended purpose" according to its labeling. That purpose is only what the device does, however, not what it is for. Thus, European requirements are related to safety and performance rather than to safety and effectiveness as in the US system (Kaplan et al., 2004). Many EU countries have incorporated an effectiveness standard (cost-effectiveness or cost-benefit) into purchasing decisions by healthcare insurance systems.

Essential Requirements

The three directives also lay out the essential requirements that apply to every medical device whatever its class. The essential requirements are a set of safety and quality standards for how a device must perform and be produced. Any device that meets the essential requirements laid out in the directives can receive the CE Marking¹³ and be distributed and sold in any member state. The essential requirements are intended to protect the health and safety of patients and providers while ensuring that there are no internal obstacles to trade within the European Community. They begin with general provisions that lay out the overall standards of safety and move into more specific requirements regarding manufacturing and labeling. Although the general provisions of essential requirements differ slightly among the categories of devices, they cover the same main points:

- A device must not cause harm to the patient, operator, or others.
- A device must do what the manufacturer says it does.
- A device must be packaged in such a way that transport does not compromise safety or effectiveness.
- A device must be able to withstand ordinary rigors of use throughout its lifetime without compromising safety or effectiveness.
- Any undesirable side effect must constitute an acceptable risk when weighed against the intended performance.

The more specific essential requirements cover design and construction of a device. These detailed requirements cover every aspect of production and the device, including chemical, physical, and biologic properties; intended and unintended radiation; and labeling.

The manufacturer must ensure that its device complies with all the essential requirements that apply to it. To do so, it may choose to provide evidence that the device meets the requirements of one or more technical standards (the use of standards in this manner is voluntary). If the manufacturer chooses to comply with a standard that is recognized by the European Commission as offering “presumption of conformity” with one or more essential requirements (known as harmonized standards), the regulatory authority (RA) or conformity assessment body (CAB) is required only to determine that evidence of compliance with the standard exists. If the manufacturer uses a different standard, one that is not “harmonized,” the RA/CAB must determine that the manufacturer had evidence that the device complies

¹³The CE Marking is a standardized logo that appears on a wide variety of consumer products sold within the European Community. It signifies that a product is one that is subject to communitywide regulation and that it has met all the standards laid out in the applicable legislation.

with the essential requirement itself. Harmonized standards are developed and issued by the European Committee for Standardization (CEN) and in some cases the European Committee for Electrotechnical Standardization. Those two committees are responsible for writing the standards that deal with both entire classes of products and specific products. In some cases, the standards are adopted wholesale from the International Organization for Standardization (ISO). Manufacturers are free to use whatever standards they like, but if their devices meet the CEN or, where applicable, ISO standards, they are judged to have met the essential requirements—often the easiest path to approval.

Risk Classification¹⁴

A device is assigned to one of four groups, or classes, by using a set of rules that take into account the potential of the device to cause harm to a patient or user. This system is referred to as a “risk-based classification scheme” although it does not take into account the probability that harm will occur by modifying evidence requirements at the conformity-assessment stage. Risk is determined on the basis of the risk associated with the use of the device, whether the device is invasive, and the length of time it is in contact with the body (Table 6-1) (Chai, 2000). It is incumbent on the manufacturer to determine the level of risk associated with a device on the basis of the specifications laid out in Annex IX of the MDD (Grubb et al., 2011). As in the FDA classification system, there are three risk classes, and subdivisions of classes to delineate the magnitude of risk further.

Class I devices are noninvasive, with some exceptions, and are judged to be of low risk. There is no explicit subdivision of products within Class I, but devices that are sterile or have a measuring function require greater oversight. Manufacturers are able to market Class I products that are non-sterile and do not have a measuring function without oversight from a notified body (NB, defined below) but must keep documentation and technical specifications available for audit on request. Class I devices that are sterile or have a measuring function must be certified by an NB (Chai, 2000).

Class II devices are divided into Class IIa and Class IIb. Class IIa devices require the involvement of an NB at the production stage but not the design phase. Class IIb devices are judged to have the potential to be of high risk and require NB approval at the design and manufacturing phases.

Class III devices are deemed to be of high risk and require “explicit prior authorization” from an NB for all phases of development and production (European Commission, 1998). Manufacturers can also turn to guidance

¹⁴The essential requirements, classification rules, and conformity-assessment procedures are substantially different for *in vitro* diagnostic medical devices, which are regulated under their own directive. Some of the information in the following sections does not apply to these devices.

TABLE 6-1 European Commission Risk Classification Scheme

Class I (low risk)	Noninvasive devices except devices that are intended to store or channel blood, body liquids, or tissues to be introduced to the body at a later time
Class IIa (medium risk)	Invasive devices intended for transient (<60 min) or short-term (<30 days) use except devices used to examine ear, nose, mouth, and throat, which are in Class I; all surgically invasive devices intended for transient use unless they emit radiation or have a biologic effect, in which case they are in Class IIb
Class IIb (medium to high risk)	Surgically invasive devices for short-term or transient use if they have a biologic effect, emit radiation, or administer medicines except devices that have direct contact with the heart or central circulatory system or central nervous system, in which case they are in Class III; all implantable or surgically invasive long-term (>30 days) devices unless they are placed in the teeth (in which case they are in Class IIa) or have contact with the heart, central circulatory system, or central nervous system (in which case they are in Class III); all devices intended to prevent conception or sexually transmitted disease unless they are implantable or long-term invasive devices (in which case they are in Class III)
Class III (high risk)	All invasive surgical devices, whether for short-term or long-term use, that come into contact with the heart, central circulatory system, or central nervous system; all implantable or long-term invasive devices that have a biologic effect, are absorbed, or undergo chemical change in the body; all implantable or long-term invasive devices intended to prevent conception or sexually transmitted disease; all devices that use animal tissues or derivatives except where they come into contact only with skin

documents released by the overseeing body in the European Commission, the Directorate-General Health and Consumer that provide detailed instructions on classifying devices, including diagrams and examples. The guidance is not legally binding but is provided for clarification purposes (European Commission, 2010a).

Notified Bodies

The directives contain provisions for the establishment of NBs, the backbone of the European regulatory structure for medical devices. An NB is a third-party private organization that is responsible for ensuring that a device meets the essential requirements laid out in the legislation. Each

member state designates a competent authority (CA), an official government regulator, that is required to oversee the accreditation and designation of third-party organizations that will perform conformity assessments and various other tasks. The CA then notifies the European Commission and the other member states as to which private organizations have been judged to be competent according to the standards laid out in the directives and for which tasks. The commission maintains an updated list of the NBs and makes this information available to the public through the New Approach Notified and Designated Organisations Web site (NANDO, 2011). NBs are accredited under individual directives, and their number varies by directive. For example, although more than 70 NBs are accredited to examine products under the MDD, only 19 are accredited for devices covered by the more specialized AIMDD (NANDO, 2011). The NBs compete with one another in that any manufacturer can go to any accredited NB in any member state and receive a CE marking.

NBs must adhere to standards regarding conflict of interest and financial incentives. NBs must be independent of manufacturers. Directors and assessment and verification staff must not be involved in the development of the device in question, nor can they represent any party involved in its development. Their compensation structure must not depend on the results of their evaluations or on the number of verifications that they provide. They must have the necessary staff and facilities to assess properly the devices for which they are designated. Any subcontractors retained by an NB must also meet all these requirements.

Although an NB is responsible for ensuring a device's conformity with the essential requirements, it also has a contractual relationship with the manufacturer, which pays for the work. That affords some protection to the manufacturer because, in theory, an NB that is inefficient or difficult to deal with will soon find itself without any customers. The accreditation procedures and standards of the European Commission ensure that the standards of safety are met, and the private status of the NB ensures efficiency and consistency for the manufacturer.

As noted above, the level of involvement of an NB is determined by the classification of the product (Table 6-2).

The NB has the responsibility to inform the CA if it withdraws a design examination certificate from the manufacturer. The CA then ensures that the device is withdrawn from the market. However, the manufacturer has the right to respond to a decision to restrict or withdraw a device before it goes into effect unless there is an urgent need to take such a step.

TABLE 6-2 Conformity Assessment Procedure by Class

Class I	Manufacturer certifies that product meets essential requirements without involvement of an NB unless device has measuring function or is sterile; documentation of product specification must be kept for auditing purposes; Class I devices must be registered with a member state
Class IIa	Manufacturer prepares technical documentation to support a “declaration of conformity” and makes it available to the NB for inspection and adopts a quality-management system that applies to manufacturing and is subject to audit by the NB, or manufacturer adopts a full quality-management system that applies to both manufacturing and design control and is subject to audit by the NB
Class IIb	Manufacturer submits to type examination by an NB in which representative sample of product along with relevant technical documentation is examined to ensure that it fulfills essential requirements and adopts a quality-management system that applies to manufacturing and is subject to audit by the NB, or manufacturer adopts a full quality-management system that applies to both manufacturing and design control and is subject to audit by the NB
Class III and Active Implantable Devices	Manufacturer submits to type examination by an NB in which representative sample of product with relevant technical documentation is examined to ensure that it fulfills essential requirements and adopts a quality-management system that applies to manufacturing and is subject to audit by the NB, or manufacturer adopts a full quality-management system that applies to both manufacturing and design control and is subject to audit by the NB; NB also examines design dossier and issues a certificate to confirm that the device complies with all relevant essential requirements

Postmarket Vigilance

In addition to the postmarketing surveillance functions of the NBs, the MDD mandated the establishment of a European Databank on Medical Devices, a centralized database containing information on manufacturers, devices, conformity assessments and certificates, and clinical investigations. Its use is currently voluntary but will be required of member states in 2011 (European Commission, 2010c). The committee is not aware of any comprehensive evaluations of the European system based on postmarketing surveillance or adverse-event reports.

The Global Harmonization Task Force

The multinational nature of medical-device manufacturing and distribution has led governments, consumers, and industry to recognize the need for international cooperation regarding medical devices. In 1992, regulatory bodies and industry of the leading medical-device producer and consumer nations—Canada, the European Union/European Free Trade Association, Japan, Australia, and the United States—formed the GHTF. A collaborative body whose purpose is to improve public health and safety, promote international trade, and provide guidance to countries with developing medical-device regulatory systems, the GHTF works to form consensus among the partners on regulatory and technical standards and postmarketing surveillance efforts. Many international agreements are in place regarding medical devices and their regulatory requirements for importation. The GHTF is an attempt to bring nations that tightly regulate medical devices into line with one another to ease the flow of devices between countries, manufacturers, and consumers while ensuring safety. In addition to participants from the founding members, the task force includes participants from non-founding members and liaison bodies, which include public-health organizations and international standard-setting organizations.¹⁵

The GHTF is structured around five study groups that are responsible for examining different issues and different paths and barriers to harmonization within them. The study groups, made up of geographically diverse members from government and industry, are (GHTF, 2008)

- Study Group 1—medical-device regulatory systems, paths to harmonization, and standards for premarket submissions and labeling.
- Study Group 2—adverse-incident reporting, postmarketing surveillance, and harmonizing data-collection and reporting systems.
- Study Group 3—existing quality-system requirements.
- Study Group 4—quality-system auditing practices.
- Study Group 5—clinical safety and performance.

To date, the study groups have released 31 final documents providing technical guidance and standardized definitions and outlining generally agreed-on principles for use by regulators and manufacturers worldwide (GHTF, 2009). The GHTF has met with mixed success in its efforts. For example, the Summary Technical Document (STED) guidance is intended to

¹⁵In March 2011, the Steering Committee Chair of the GHTF announced that the organization would be developing and transitioning to a “regulator-led harmonisation and collaboration group.” According to the statement, the new entity would focus primarily on regulators of medical devices, including seeking new members in order to more accurately reflect the current medical-device market, while continuing to value input from industry and other stakeholders as appropriate (GHTF, 2011).

standardize the format whereby a manufacturer submits technical information to a regulatory authority or conformity-assessment body (such as an NB). STED would allow manufacturers to save time and effort in preparing a product for market and allow better comparison and information-sharing among regulatory jurisdictions. Although the STED guidance has been adopted or implemented as a pilot program in all five GHTF founding-member jurisdictions, it has not been widely used (IOM, 2010). Nations that have highly developed regulatory frameworks agree in principle that harmonization is desirable, but differences in legal systems and regulatory cultures make implementation challenging.

The Summary Technical Document Program

In 2002, GHTF Study Group 1 proposed a pilot program for device premarket review known as the Summary Technical Document (STED), program (GHTF, 2008). The FDA then issued draft guidance to assist the medical-device industry and FDA staff in implementing a voluntary pilot program (FDA, 2005b). Not all devices are eligible to participate in the pilot. Eligible devices are limited to those which are seen to be the subjects of common and substantial interest by the member countries of the GHTF.¹⁶

The program, begun in June 2003, is intended to evaluate STED as an alternative premarket submissions process. Its objective is to decrease the regulatory burden and increase the efficiency of the approval process for manufacturers that operate within the international market (FDA, 2005b; GHTF, 2008). Industry groups have stated their support for the STED program, but the FDA has identified only 27 STED submissions¹⁷ (IOM, 2010). Of the submissions, 24 were 510(k) submissions, and 3 were PMA applications. The PMA applications were all approved. Of the 510(k) submissions, 20 resulted in a determination of substantial equivalence, 2 were not substantially equivalent, and 2 were withdrawn. Given the lack of data needed to evaluate the program and the small number of devices eligible, it is not possible to determine what factors contribute to the lack of industry participation in the program.

Finding 6-8 Other countries that tightly regulate medical devices do not rely solely on substantial equivalence to a predicate for premar-

¹⁶A list of eligible devices and information on the alternative format (developed by the Global Harmonization Task Force) can be found in Appendix C of the Guidance on Traditional and Abbreviated 510(k)s.

¹⁷The FDA's Document Mail Center identifies all submissions on receipt. STED submissions are flagged in the system. However, the FDA has stated that there are limitations in the system, and that the data on STED submissions may not be accurate (e-mail from Philip R. Desjardins, FDA, January 7, 2011).

ket review of medium-risk devices. The Global Harmonization Task Force also does not offer as part of its guidance a predicate-based system for premarket review of medical devices.

SUMMARY OF FINDINGS

The Growing Number and Complexity of Medical Devices

- Finding 6-1 Medical-device technologies have evolved rapidly, and devices have become increasingly complex since the 1976 Medical Device Amendments.
- Finding 6-2 Manufacturers are using increasing amounts of software in devices and as devices; the increase is expected to continue. Software offers many benefits over hardware, including flexibility, ease of change, and the possibility of use in other devices.
- Finding 6-3 Software is responsible for an increasing number of recalls. There are insufficient data, however, to determine whether the increase reflects the increasing proportion of software in medical devices or a new and different set of problems and vulnerabilities.
- Finding 6-4 Software is different from hardware and therefore requires a different kind of evaluation.

The Medical-Device Ecosystem

- Finding 6-5 Industry-funded assessments of the effects of the 510(k) clearance process report that implementation of the process leads to a lack of predictability and transparency, which in turn has an adverse effect on venture-capital investment.
- Finding 6-6 The committee did not find assessments of how much and in which way innovation is influenced by the 510(k) clearance process.
- Finding 6-7 There is little collaboration in collection of postmarketing surveillance data among the FDA, healthcare facilities, healthcare providers, the medical-device industry, professional societies, payers, and patient-advocacy groups.

Globalization of the Medical-Device Industry

- Finding 6-8 Other countries that tightly regulate medical devices do not rely solely on substantial equivalence to a predicate for premarket review of medium-risk devices. The Global Harmonization Task Force also does not offer as part of its guidance a predicate-based system for premarket review of medical devices.

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7

Conclusions and Recommendations

As noted in Chapter 1, the committee was charged by the Food and Drug Administration (FDA) to review the 510(k) clearance process and answer two principal questions: Does the current 510(k) clearance process optimally protect patients and promote innovation in support of public health? If not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) clearance process optimally? To address its charge, the committee took a multipronged approach in its evaluation of the 510(k) clearance process, as summarized in Chapters 2–6. Aspects of the 510(k) process and other relevant factors that were evaluated include the following:

- The legislative history of the 510(k) process.
- The 510(k) regulatory framework that resulted from legislation.
- How the 510(k) process fits into the larger medical-device regulatory framework. (The 510(k) clearance process is an integrated component of the larger medical-device regulatory framework. The committee elected to evaluate the 510(k) program in the context of this larger framework.)
- How the 510(k) process is currently implemented by the FDA.
- Available postmarket information on the safety and effectiveness of 510(k)-cleared devices.
- Other factors that affect medical-device regulation (for example, the process of innovation and the medical-device ecosystem in the United States and in other jurisdictions).

The body of evidence gathered from the committee's evaluations influenced its deliberations. The conclusions and recommendations presented in this chapter are the results of the committee's deliberations.

PROTECTING THE PUBLIC'S HEALTH BY ENSURING THE SAFETY AND EFFECTIVENESS OF MEDICAL DEVICES

To assess whether the 510(k) clearance process is protecting the public's health by providing reasonable assurance that marketed Class II medical devices are safe and effective, the committee explored two avenues. The committee studied 510(k)-related legislation to determine whether the statute governing the 510(k) program provides for the FDA's goals for this program (described below). The committee also evaluated available information on the safety and effectiveness of marketed medical devices.

The Regulatory Framework of the 510(k) Program

As outlined in Chapters 2 and 4, the committee found a substantial disconnect among the committee's statement of task, the Center for Devices and Radiological Health (CDRH) statement of the goals of the 510(k) clearance process, and the FDA's statute governing the 510(k) clearance process. The committee's statement of task reads:

The current 510(k) process reflects the statutory framework and the U.S. Food and Drug Administration's (FDA) implementation of the framework; it is intended to meet two important goals: 1) make available to consumers devices that are safe and effective, and 2) promote innovation in the medical device industry.

Similar language describing the goals of the 510(k) process are included in the *CDRH Preliminary Internal Evaluations, Volume 1—510(k) Working Group Preliminary Report and Recommendations* (FDA, 2010a, 128), which states that

the aim of the 510(k) program is two-fold: (1) to assure, through a quality review process, that marketed devices, subject to general and applicable special controls, provide a reasonable assurance of safety and effectiveness; and (2) to foster innovation.

However laudable those goals may be, they are not the purposes that Congress embedded in the 510(k) program (Findings 2-2 and 2-5).

In practice, the assessment of substantial equivalence generally does not require evidence of safety or effectiveness of a device. Unlike the premarket approval (PMA) process, by law the 510(k) process, with some exceptions

(discussed below), focuses solely on the determination of a device's substantial equivalence to a predicate device. According to the FDA and the Supreme Court, when the FDA finds a device substantially equivalent to a predicate device, it has done no more than find that the new device is as safe and effective as the predicate (OTA, 1984, p. 128).¹ It is important to note that individual devices on the market before the enactment of the 1976 Medical Device Amendments (MDA)—the origin of all predicate devices for the 510(k) process—have never been systematically assessed to determine their safety and effectiveness (Finding 2-1). The FDA created advisory panels to assist in the device classification process. These panels reviewed information on the risks posed by types of devices, including the potential risks resulting from a failure of lack of effectiveness, and recommended into which class the device type should be placed, in order to provide a reasonable assurance of safety and effectiveness. Neither the panels nor the FDA itself undertook an assessment of the clinical safety or effectiveness of individual devices during the original classification process. Because the preamendment device to which equivalence was established was not itself reviewed for safety or effectiveness, the committee found that clearance of a 510(k) submission was not a determination that the cleared device was safe or effective (Finding 4-1).

Under the Safe Medical Devices Act of 1990, the FDA is permitted to require evidence of safety and effectiveness, including clinical studies, when it is necessary for determining whether a difference in technologic characteristics between a new device and its predicate renders the new device less safe or effective than the predicate or raises different questions of safety and effectiveness from the predicate. If, despite the change in technologic characteristics, the new device is as safe and effective as the predicate, it will be found substantially equivalent.

Nearly all 510(k) submissions for devices that have new technologic characteristics receive a determination of substantial equivalence. About 15% of Class II and Class III 510(k) submissions for which the FDA reached a determination of substantially equivalent or not substantially equivalent in FY 2005–2007 had new technologic characteristics (GAO, 2009a). Some 99.5% received a determination of substantially equivalent.

The 510(k) clearance process has evolved from 1976 to the present through administrative and legislative changes, narrowing the array of issues that the FDA may consider in a 510(k) review, and limiting the type of evidence the FDA could require. Throughout the entire period, there has

¹Memorandum Re: Internal Control Weaknesses in the Food and Drug Administration's Medical Device 510(k) Review Process, from the HHS inspector general to the HHS assistant secretary for health (July 5, 1990) 1, fn. 1; Brief for the United States as Amicus Curiae Supporting Respondents/Cross-Petitioners 19-20, *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) (No. 95-754) (some internal citations omitted); *Lohr*, 518 U.S. at 493-94 (citations omitted).

been a high frequency of finding of substantial equivalence (Finding 2-6). Furthermore, the gap in relative burdens on manufacturers between the 510(k) process and the PMA process created by the 1976 MDA has been maintained by administrative and legislative changes, which have encouraged preferential use of the 510(k) process (Finding 2-7).

Available Recall Data on 510(k)-Cleared Devices

The committee explored FDA recalls of medical devices as a potential indicator of their safety and effectiveness. Proponents of the 510(k) clearance process have cited the low number of Class I recalls associated with 510(k)-cleared devices as an indication of the safety of devices on the market. (The FDA classifies recalls in reverse order of device classes. Class I recalls denote the greatest immediate risk to the health, whereas Class I devices present the lowest inherent risk to health.) In contrast, consumer-protection advocates have cited several high-profile medical-device safety issues, some reported in the mass media, as evidence that premarket review via the 510(k) process is inadequate. They have expressed concern that the FDA's ability to recall problematic medical devices cleared through the 510(k) process is insufficient (Bloomberg News, 2008; Harris, 2010a, 2010b; Hines et al., 2010; Meier, 2010; Mundy and Favole, 2009; Shuren, 2010; Stein, 2010; Zuckerman et al., 2011).

Although the committee cites recall data in this report, it recognizes that using these data as an indicator of device safety and effectiveness has several shortcomings. The committee also recognizes that mass-media reports of problematic medical devices that were cleared through the 510(k) clearance process do not necessarily represent generalizable evidence about the soundness of the entire 510(k) program.

The committee does not believe that there is a public-health crisis related to unsafe or ineffective medical devices. The committee found that available postmarketing-surveillance data do not provide sufficient information about potential harm or lack of effectiveness to be a useful source of data about the safety and effectiveness of marketed devices (Finding 5-2). As noted in Finding 2-1, although the safety and effectiveness of preamendment Class II devices has not been systematically reviewed, their continued use in clinical practice provides at least a level of confidence in their safety and effectiveness.

Does the 510(k) Clearance Process Provide a Reasonable Assurance of Safety and Effectiveness?

The committee found that the 510(k) program lacks the statutory basis to make it a reliable premarket screen for safety and effectiveness of Class II medical devices. Therefore, the committee drew the following conclusion:

Conclusion 7-1 The 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices with some exceptions. The 510(k) process cannot be transformed into a pre-market evaluation of safety and effectiveness as long as the standard for clearance is substantial equivalence to any previously cleared device.

The committee is not suggesting that all, many, or even any medical devices cleared through the 510(k) clearance process and currently on the market are unsafe or ineffective. Rather, the committee found that the available information is insufficient to support highly confident conclusions about the safety and effectiveness of 510(k)-cleared medical devices in clinical use. As elaborated on below, the committee is concerned by the lack of information-gathering efforts to identify potential safety and effectiveness problems with devices and by the ineffectiveness of the regulatory system to respond to problems if they are identified (Finding 3-2).

FACILITATING INNOVATION IN SUPPORT OF PUBLIC HEALTH

As discussed in Chapter 6, views diverge on what constitutes innovation in medical devices. The committee agreed on a definition of *innovation* to assess whether the current 510(k) clearance process optimally protects patients and promotes innovation in support of public health. The committee believes that given the broad interpretation of the term it should define innovation not simply as a change but as a favorable change in the context of public health. The committee also believes that given the complexity of the process of innovation and the iterative and combinatorial nature of the process a broad definition would be more accurate than one that sought to create a list of specific attributes. The committee defined innovation broadly as improving the quality of, efficiency of, or access to health care.

To assess how innovation is affected by medical-device regulation, the committee studied the legislative history and implementation of the 510(k) process and findings from the medical-device industry about the effect of the 510(k) process on innovation. The committee found that the 510(k) clearance process was not designed to reward, recognize, or encourage innovation. At most, promotion of innovation was a byproduct of a process that, by minimizing unnecessary regulatory burdens, facilitated the entry

into the market of new devices that do not raise novel questions of safety or effectiveness (Finding 2-4). In reducing regulatory burdens and providing additional resources to allow for timely review, the changes in the original legislation over the past 35 years have neither forced nor rewarded innovation. Although it may be argued that such changes may improve the likelihood of innovation, it remains unclear, and the committee argues that it is indeterminable given current data, whether the legislative changes have promoted innovation.

The 510(k) clearance process is generally more economical, faster, and less burdensome than the PMA process for both industry and the FDA (Finding 3-3). Substantially fewer postmarket controls apply to 510(k)-cleared devices than to PMA devices. Since the implementation of the MDA of 1976, which created both programs, there has been a substantial difference between the 510(k) process and the PMA process in premarket requirements. The committee found that over the past 35 years legislative and administrative changes in the 510(k) program have maintained that gap in requirements between the 510(k) and PMA programs. The disparity in program requirements, costs, and postmarket requirements encourages preferential use of the 510(k) process (Finding 2-7). Although the 510(k) clearance process offers a less burdensome pathway to market, the increasing complexity of devices is challenging the capabilities of this process (Findings 6-1, 6-2, 6-3, and 6-4). The committee believes that a regulatory pathway based on demonstrating substantial equivalence to predicate devices is not a rigorous scientific means of adapting to new and increasingly complex types of technology.

Several assessments of the 510(k) program conclude that the FDA's implementation of the program, not the underlying process itself, has stifled innovation because of a lack of transparency and predictability, which has led to an adverse effect on venture-capital investment in future medical-device development (Finding 6-5). Typical measures used in those assessments are the ease of premarket review and relative speed to market compared with the European Union premarket process (Ernst and Young, 2009; Lewin Group, 2010; Makower et al., 2010; MDMA and NVCA, 2009; PwC and BIOCOM, 2010). The committee, however, does not believe that such factors as ease of premarket review and relative speed to market are surrogates for innovation.

The FDA has procedures to develop, adopt, and implement guidance and standards. It is persistently hindered, however, in fully developing these materials by a lack of or limitations in human, fiscal, and technologic resources and capabilities (Finding 3-4). Confusion regarding key regulatory phrases (for example, *intended use* and *indications for use*) has created uncertainty about the decision-making process (Finding 4-3). The process also is restricted in how it evaluates devices in that it currently does not

recognize the distinction between devices cleared as tools and devices cleared for specific clinical applications (Finding 4-4). Those factors create confusion regarding the types of questions asked by reviewers and the types of information needed in premarket submissions.

In its *Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations*, CDRH identified several institutional, structural, and resource concerns regarding the timely incorporation of new science in premarket review (FDA, 2010b). The report found that the

CDRH has not yet articulated a business process to be followed across the Center for evaluating new scientific information and determining when that information warrants certain types of action, such as a change in premarket evidentiary expectations.

The *Utilization of Science* report also states that CDRH finds it challenging to communicate changes in regulatory thinking both within the agency and externally in response to new information and that this challenge affects all stakeholders. Industry representatives have expressed concern about the increasingly required use of clinical data in the 510(k) review. The committee's evaluation found that the FDA has provided inconsistent guidance in determining the need for clinical data, the type of data, and the manner in which data, if available, should be integrated into the decision-making process (Finding 4-8). The lack of clear guidance affects the timeliness and consistency of 510(k) device submissions provided by industry and the ability of reviewers to evaluate them.

Does the 510(k) Clearance Process Promote Innovation in Support of Public Health?

On the basis of the above findings, the committee was unable to determine whether the 510(k) clearance process is facilitating or inhibiting innovation. Therefore, the committee concludes as follows:

Conclusion 7-2 Information that would allow an understanding of the extent to which the 510(k) clearance process facilitates or inhibits innovation does not exist.

The committee believes that although the regulatory process can facilitate innovation that improves public health by making safe and effective Class II medical devices available to consumers in a timely manner, the FDA should not be the arbitrator of what constitutes innovation, nor should it seek to channel device development and premarket review toward agency-determined public-health priorities. In the committee's opinion, the FDA's

role in facilitating innovation in Class II medical devices through premarket review should be to create a regulatory framework that sets appropriate thresholds for bringing products to the market. The thresholds should be stringent enough to satisfy the agency's objective of ensuring that marketed medical devices will be safe and effective throughout their life cycles but realistic enough to permit timely entry of new devices that may offer improvements over already marketed devices. Rather than be charged with *promoting* innovation, the committee believes that the FDA should seek to *facilitate* it, ensuring that the premarket review of Class II devices does not needlessly *inhibit* innovation.

RECOMMENDATIONS

On the basis of the above conclusions, the committee offers the following recommendations aimed at improving regulation of Class II medical devices.

Recommendation 7-1 The Food and Drug Administration should obtain adequate information to inform the design of a new medical-device regulatory framework for Class II devices so that the current 510(k) process, in which the standard for clearance is substantial equivalence to previously cleared devices, can be replaced with an integrated premarket and postmarket regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle. Once adequate information is available to design an appropriate medical-device regulatory framework, Congress should enact legislation to do so.

The committee believes that a move away from the 510(k) clearance process should occur as soon as reasonably possible but recognizes that it will take time to obtain the information needed to design the new framework.

It is essential that the new regulatory framework be based on sound science. The committee does not believe that available information is adequate to inform the design of an appropriate framework. Nor does the committee believe that the new framework should be developed in isolation from other components of the FDA's medical-device regulatory system. In developing the new framework for Class II devices, the efficiency, cost, and effectiveness of the PMA process should be evaluated. The FDA should carefully consider what types of evidence are necessary to demonstrate a reasonable assurance of safety and effectiveness in the new framework. It is beyond the committee's scope of work to detail those types of evidence. The committee believes that it may be possible for the performance of comparative devices

to be a component of the evidentiary materials supporting a claim of safety and effectiveness of Class II devices.

The FDA should be clear that its role in facilitating innovation in medical devices is to develop regulatory thresholds that are rigorous enough to satisfy the agency's primary objective of ensuring that marketed medical devices will be safe and effective throughout their life cycles but realistic enough to permit timely entry of new devices into the market.

On the basis of its findings, the committee identified several topics to which the FDA should give particular consideration as it develops a new framework. A number of existing and emerging technologies (for example, combination products, software, nanotechnology, and medical robotics) merit detailed thought as part the development of the new framework. The FDA should consider integrating some elements of the quality-system regulations, especially those related to design controls and product-release criteria, into the premarket review process of the new framework to demonstrate that devices will perform as represented by their manufacturers. The FDA should also consider, as part of the new framework, including a more extensive review of device labeling and a system to track labeling changes.

A comprehensive review of the successes and problems of device regulation over the past 35 years would better inform the FDA and Congress as to whether and how to change the overall regulatory structure for devices. Finally, medical-device regulatory systems in other countries and jurisdictions should be evaluated to determine whether components of those systems could inform the design of the new regulatory framework in the United States. The committee notes that medical-device regulatory systems in other countries that have robust medical-device markets do not use substantial equivalence to predicates as the standard for approval for marketing (Finding 6-8).

The committee urges the FDA to create a regulatory framework that more closely matches the ideal regulatory framework outlined by the committee in Chapter 1. The attributes of this regulatory framework are as follows. They are not presented in any priority order.

- The process should be based on sound science.
- The process should be clear, predictable, straightforward, and fair.
- The process should be self-sustaining and self-improving.
- The process should facilitate innovation that improves public health by making medical devices available in a timely manner and ensuring their safety and effectiveness throughout their life cycle.
- The process should apply relevant and appropriate regulatory authorities and standards throughout the life cycle to ensure safety and effectiveness.
- The process should be risk-based.

FDA staff at all levels, the medical-device industry, consumers, health-care providers, payers, and Congress must play a role in the development of the proposed regulatory framework.

The committee does not believe that further investment in the 510(k) process is a wise use of the FDA's scarce resources and is not recommending specific changes in the 510(k) clearance process itself. Instead, it believes that the FDA's resources would be put to better use in addressing problems with other components of the medical-device regulatory framework and with the FDA's decision-making processes and obtaining information needed to develop a new framework for Class II medical devices. The committee's recommendations for accomplishing those goals are detailed below. The committee recognizes that scarce resources in the FDA could affect its ability to implement these recommendations. Therefore, it has directed the recommendations toward activities that are useful in both the short term and the long term and that conserve scarce resources.

The committee recommends that the FDA promptly implement Recommendations 7-2 to 7-8, found below. The committee believes that following these recommendations will allow the FDA to

- Develop the information base on which to establish the new regulatory framework.
- Address problems with postmarketing surveillance and with use of postmarket regulatory authorities.
- Develop and implement a continuous quality-improvement system in CDRH.

Postmarketing Surveillance

As stated repeatedly in the report, the 510(k) clearance process is not a stand-alone program but a component of the larger medical-device regulatory framework. As part of that framework, the 510(k) program depends on the effectiveness of other regulatory components. The committee found weakness in postmarketing surveillance of medical devices (Findings 4-5, 4-6, 5-1 to 5-7, and 6-7).

The committee found evidence that the FDA's postmarketing surveillance systems, as well as other postmarket activities, often do not provide sufficient information about potential harm or lack of effectiveness of marketed devices (Findings 4-5 and 5-2). The FDA's active postmarketing surveillance programs, such as MedSun and MD EpiNet, have potential but will require stable, adequate resources and resolution of various technical issues to achieve their full promise (Finding 5-5). The FDA is including medical devices in the Sentinel Initiative; additional investment will be needed to develop a rich source of clinical data on medical devices. The FDA's device

postmarketing surveillance programs have been adversely affected by the instability of the agency's congressional financing. Moreover, user fees can be used only for premarket activities (Finding 2-8). Non-FDA postmarketing surveillance activities, such as privately funded device registries, are potentially important sources of performance information, but currently only selected device types are studied, and the lack of standardization in how information is collected and reported persists (Findings 5-6 and 5-7). Finally, there is little collaboration in collection of postmarketing surveillance data among the FDA, healthcare facilities, healthcare providers, the medical-device industry, professional societies, payers, and patient-advocacy groups (Finding 6-7).

The inadequate postmarketing surveillance systems—both those in the FDA and those which are privately funded—and the resulting lack of useful, consistent, and reliable data make it impossible to draw confident conclusions about the performance of medical devices now on the market.

Recommendation 7-2 The Food and Drug Administration should develop and implement a comprehensive strategy to collect, analyze, and act on medical-device postmarket performance information.

The FDA should give high priority to postmarketing surveillance because it is an invaluable investment in short-term and long-term medical-device safety oversight and assessment of device effectiveness. As discussed in Chapter 5 of this report, the committee found that there was no long-term strategy in the FDA to address the effectiveness of medical-device postmarketing surveillance. The committee recommends that the FDA develop a postmarketing surveillance strategy to meet the following objectives: provide performance information for use in the premarket review process, inform the development and use of postmarketing tools (that is, general and special controls) to better manage the risk-benefit ratio throughout the life cycle of devices, and inform the design of a new regulatory framework. To meet those objectives, the FDA should

- Explore how to better understand potential device risks better with existing postmarket tools, such as device tracking and Section 522 surveillance studies.
- Expand collaborative relationships with existing non-FDA medical-device data sources and encourage standardization of processes and systems to increase efficiency and the ability of all parties to use the data.
- Institutionalize integration of premarket and postmarket data systems.

- Identify methods for learning from independent clinical research reported in the peer-reviewed literature on poor or adverse health outcomes related to devices that may warrant FDA action.
- Revise its strategy to communicate more effectively with consumers, providers, and the public about problems with the performance of medical devices.

The committee acknowledges that the traditional administrative and clinical data sources used for surveillance of drugs may not be appropriate for surveillance of medical devices, particularly surveillance of Class II devices. Device surveillance will probably require other data sources, such as unique device identifiers (discussed in Chapter 5).

Congress should support the capacity of CDRH's postmarketing surveillance programs by providing stable and adequate funding.

Postmarket Regulatory Authorities

When the FDA discovers violations of the law or products that pose unacceptable risks to consumers, it has a wide variety of authorities (or tools) available to remedy the situation and to sanction the violators. The committee found that the agency uses these authorities sparingly (Findings 3-1 and 3-2). Although the committee identified the procedural requirements that the FDA must fulfill to exercise the authorities, the requirements do not in themselves appear to explain CDRH's perception that there are "important limitations" on the use of postmarket tools.

Recommendation 7-3 The Food and Drug Administration should review its postmarket regulatory authorities for medical devices to identify existing limitations on their use and to determine how the limitations can be addressed.

The appropriate use of postmarket regulatory authorities is an essential component of a successful medical-device regulatory program. The FDA should analyze barriers to efficient and effective use of these authorities and identify means to mitigate the barriers. It is especially important that the FDA be able to use the authorities, when needed, because a 510(k) decision made by the FDA establishes a new predicate device that is legally binding unless and until the agency has rescinded the decision or has barred the device covered by that decision from the market through other legal actions (Finding 2-3).

If required, Congress should pass legislation to remove unnecessary barriers to the FDA's use of postmarket regulatory authorities.

A Modified De Novo Process

The committee believes that the de novo process offers a potential basis of a better regulatory model for premarket review of Class II devices. In its current state, however, the de novo process is time-consuming and difficult for both the FDA and manufacturers to navigate (Finding 4-9).

Recommendation 7-4 The Food and Drug Administration should investigate the viability of a modified de novo process as a mechanism for evaluating the safety and effectiveness of Class II devices.

A pilot program of a modified de novo process would allow the FDA to determine the feasibility of the modified process as a replacement for the 510(k) clearance process. The 1976 MDA states that general controls alone are not sufficient to ensure the safety and effectiveness of Class II devices. Therefore, as part of a modified de novo process, the FDA should explore ways to expedite development of special controls, develop guidances, and adopt standards for devices. The agency also should consider expanded use of external expertise and preinvestigational device exemption meetings with submitters and use of conditional clearances for devices on which there is little premarket performance information (such as a clearance conditioned on postmarketing surveillance or use of registries).

The success of the modified de novo process will depend on CDRH's ability to develop a rich database on its processes and performance. Therefore, it is imperative that CDRH develop a comprehensive information-technology strategy based on an assessment of program needs and practices.

A Continuous Quality-Improvement Program

The committee's assessment of the 510(k) clearance process showed that CDRH's operations lack a continuous quality-assurance process (Finding 3-5). CDRH's Task Force on the Utilization of Science in Regulatory Decision Making found that the center did not have a process for addressing the use of new types of scientific information in regulating medical devices (FDA, 2010b). Lack of such a process prevents CDRH from effectively addressing new issues as they arise and from developing a long-term vision of the center and its mission. For example, the Government Accountability Office found that CDRH does not have a comprehensive information-technology strategic plan that would allow it to meet its needs as it modernizes (GAO, 2009b).

Recommendation 7-5 The Food and Drug Administration should develop and implement a program of continuous quality-improvement to track regulatory decisions on medical devices, identify potential

process improvements in the medical device regulatory framework, and address emerging issues that affect decision-making.

Throughout the report, the committee identifies evidence that the inadequate information technology and management infrastructure in CDRH affects not only the 510(k) program but also the center's other programs. For example, because data systems in the FDA are inadequate, the agency does not have the ability to trace the history of 510(k) decisions (Finding 4-2). Those 510(k) clearances are legally binding on CDRH for making future decisions about devices going through the 510(k) clearance process. Thus, any unsafe or ineffective devices are embedded in the system and as both a legal and a practical matter may be used as predicates for new products until they are removed from the market. Removing those devices from the market may be difficult because there is no systematic way to identify them. By developing a business model grounded in continuous quality-improvement, CDRH will be able to identify problems and develop the information and capacity to address them in a data-driven, transparent manner.

Facilitating Innovation in the Medical-Device Industry

As stated above, the committee believes that the FDA's role in facilitating innovation with respect to Class II devices is to create and enforce a regulatory framework where the threshold to market provides reasonable assurance that medical devices are safe and effective throughout their life cycle while permitting timely entry of new devices that may offer improvements over already marketed devices. The committee did not find assessments of how much and in what way (that is, facilitating or inhibiting) innovation is influenced by the 510(k) clearance process (Finding 6-6).

Recommendation 7-6 The Food and Drug Administration should commission an assessment to determine the effect of its regulatory process for Class II devices on facilitating or inhibiting innovation in the medical-device industry.

The recommended study should include various ways to measure innovation beyond "time to market" or the number of devices of a particular type on the market and instead focus on a broader understanding of the relationship among regulation, innovation, and patient health and safety throughout the device life cycle. There should be analysis of how incremental changes in existing devices affect clinical use, safety, and effectiveness; characterization of research and development costs for truly innovative technologies that enhance healthcare quality, efficiency, or access; estimates of the effects of government interventions (for example, subsidies, mar-

ket exclusivity, and research support); and description of the current and foreseeable relationship between FDA clearance or approval and payers' willingness to reimburse for devices.

Software

Because of software's important differences from hardware (as discussed in Chapter 6), the FDA should develop a better understanding of the roles that software plays in medical devices, analyze their potential effects on the safety and effectiveness of the devices, and insist on evidence-based procedures that ensure device safety and effectiveness. The committee believes that the FDA should review and update its guidance on software validation. Updating the guidance is important given the increasing use of software in devices and as devices (for example, medical device data systems), the integration in medical devices of commercial software not intended for use in them, the increasing uncertainty introduced by device complexity, and potentially unsafe interactions with other software systems. Reliance on "best practices" is no longer sufficient, particularly when best-practice recommendations often lag behind rapid change in software innovation. The FDA should commission an independent study focused on addressing these questions and concerns about software in medical devices. The study should include not only an analysis of potential system problems introduced by software but also recommendations about how the FDA can evaluate a device's software with respect to safety, dependability, security, reliability, and privacy.

As suggested in a National Research Council study about ensuring software dependability (NRC, 2007), the FDA should develop an evidence-based approach for use by the medical-device industry to support its claims of safety and effectiveness. Thus, one output of the present committee's recommended study should be evidential guidance to industry: What should be reported to demonstrate safety and dependability?

At present, most available information about safety and effectiveness of devices relies only on recall data; there is little specificity about the contribution of software to failures that lead to recalls. Thus, it is not always possible to understand the particular contribution of software to device quality and function; neither is it clear what oversight is needed in the premarket review process. Moreover, because software engineers learn as much from failure as from success, the scope of device-related reporting should be broadened to include not only information about software-related device failures but also descriptions of near-failures: What happened, why it happened, and what can be done to prevent such problems in the future? The information gained from such surveillance can inform the design and development of new or modified software and the review of premarket submissions.

Recommendation 7-7 The Food and Drug Administration should develop procedures that ensure the safety and effectiveness of software used in devices, software used as devices, and software used as a tool in producing devices.

Preamendment 510(k)-Eligible Class III Devices

After 35 years, the FDA has not completed the task of calling for PMAs for or reclassifying preamendment Class III device types. Until the FDA completes that task, those devices are allowed to enter the market through the 510(k) clearance process (Finding 4-7). Congress in 1990 directed the FDA to complete that task in a timely manner.² Currently 25 device types remain eligible to enter the market through the 510(k) process. The FDA has begun a five-step process to require PMAs or to reclassify those device types to a lower class (GAO, 2011). As of April 2011, the FDA has assessed the risks and benefits associated with 21 device types (step 2 of the process) and has received and reviewed public comments on 5 device types (step 4 of the process). The agency has issued a final rule for one of the 26 device types (FDA, 2011). The committee recognizes the resource constraints that have prolonged this process, but it nevertheless urges the FDA to give high priority to completing this task.

Recommendation 7-8 The Food and Drug Administration should promptly call for PMA applications for or reclassify Class III devices that remain eligible for 510(k) clearance.

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A

History of Medical-Device Legislation and Regulation in the United States

The committee was charged to review the 510(k) clearance process and to evaluate whether it protects patients optimally and promotes innovation in support of the public health. The Food and Drug Administration (FDA) strives to find an appropriate balance between promoting and protecting the public health.¹ To aid in understanding the current 510(k) system and how it evolved to its present state, this appendix outlines pertinent elements in the history of device regulation as they are related to Class II devices generally and to the 510(k) clearance process in particular.

The 510(k) system is a type of gatekeeping for managing the transfer of new technology from the laboratory to the bedside. Entering the commercial market is a single point in the life cycle of a product. The need for and rigor of premarket review are directly affected by the availability of other tools to protect patients after marketing commences. Effective postmarketing² controls can reduce the burdens of premarket review and accelerate its speed. Thus, this appendix will examine device regulation beyond the 510(k) process itself.

Of particular relevance is the safety surveillance system by which the FDA can identify and act on risks that emerge after a device enters the market. A robust and effective system might provide metrics for assessing

¹Federal Food, Drug, and Cosmetic Act, § 1003(b) (the most current version will hereinafter be referred to as FFDCA), 21 USC § 393(b) (2006).

²The appendix will use the word *postmarketing* to refer to the situation after a product enters commercial distribution. The FFDCA uses *postmarket* specifically to describe surveillance studies that FDA can order under Section 522. 21 USC § 360l (2006). To avoid confusion, *postmarket* will be used only with reference to that provision of the law.

the nature and extent of harm that is associated with products cleared or approved by the FDA and therefore indirectly reflecting on the quality of the FDA review processes. In contrast, if safety surveillance is weak and of limited scope, that injuries are not identified can yield little confidence in the review process—absence of evidence of harm is not evidence of the absence of harm. Therefore, this appendix will review the history of adverse-event monitoring of medical devices.

Consideration of the 510(k) clearance process largely involves Class II devices. Since 1997, most Class I devices have been exempted from 510(k) review. Most Class III devices are subject to FDA review through the pre-market approval (PMA) process, not the 510(k) pathway, although 25 types of Class III devices are still eligible to enter the market by the 510(k) clearance process. As recommended in Chapter 7, the committee urges the FDA to cease reliance on the 510(k) process for Class III devices as soon as possible. Once that step is completed, the 510(k) process will apply only to Class II devices—although a few are exempt from 510(k) requirements—and some Class I devices.

In considering the gatekeeping function related to the introduction of new medical products to the market, the Federal Food, Drug, and Cosmetic Act (FFDCA) has adopted a variety of approaches: no government preclearance review whatsoever, a limited preclearance review, or extensive government review. For most drug products, Congress chose detailed review and affirmative approval by the FDA before commercialization, which has led to long and expensive processes of drug development. For medical devices, however, Congress has adopted all three approaches: exemption from any premarket review by the FDA before marketing of a product; limited pre-market review through a notification of intent to market, commonly called the 510(k) submission; and thorough review and affirmative approval before launching of a product (through the PMA).

After entering the market, products continue to be subject to a variety of legal requirements and prohibitions, which are enforced primarily by the FDA. Congress has given the FDA diverse powers in a patchwork fashion, usually in response to demonstrated or alleged deficiencies in current systems.³ In medical-device terminology, the requirements are called general and special controls and apply to devices according to the degree of potential

³The laws governing medical devices have evolved separately from those applicable to drugs even though many of the authorities appropriate for one system might seem equally appropriate for the other. The nonparallel development reflects the fact that Congress often approached new issues that emerged in one field of medical products without considering whether the issues might also exist in the other. Thus, for example, with respect to medical devices Congress has given the FDA authority to order the recall of products that violate the law, to require notification of voluntary product removals, and to impose civil money penalties for violations. The FDA has none of those authorities over drugs to the same degree. Conversely, the agency has much more extensive authority over labeling, advertising, and marketing of prescription

risk presented but generally without regard to the extent of review before market entry. As with premarket review, postmarketing protections of health can affect innovation, depending on the rigidity and zeal with which the regulation with which regulations are enforced.

The history of federal regulation of medical devices reflects several important forces.

First, the FDA has legal constraints on its discretion in exercising its powers. To guarantee that the will of Congress would not be subverted by the executive branch, Congress set forth detailed instructions on how the FDA should carry out the law. The original Medical Device Amendments of 1976 more than doubled the length of the FFDCAs as it stood at that time. Later amendments added far more text than they removed. Congressional micromanagement can be found in many parts of the current law.

To ensure presidential control over executive branch activities, the FDA has been required to submit proposed major regulations and other policies to the Office of the Secretary of Health and Human Services and to the White House Office of Management and Budget (OMB) for review and approval before publication, and there are procedural requirements for public participation to safeguard interests of patients, manufacturers, and others. Federal courts review the FDA's interpretations of law, its regulations, and its actions. Judicial rulings can profoundly influence implementation of the medical-device statute.

Second, the FDA does not operate in a political vacuum but is subject to scrutiny as it carries out its mandates. Regulatory policies and philosophies change from one president to the next. Congressional committees that have jurisdiction over the FDA can attempt to drive the agency toward policies and actions that they prefer through oversight hearings, committee investigations, and reviews by the General Accounting Office (GAO, now the Government Accountability Office), formerly by the Office of Technology Assessment (no longer in existence), and by the Department of Health and Human Services inspector general.

Third, the modern history of the FDA shows a disparity between congressional mandates, under the various legislative enactments, and congressional appropriations of persistently insufficient resources (FDA Science Board, 2007, 9-10). The appropriation process is subject to its own set of pressures, such as tax and fiscal policy, competing demands for scarce federal revenues, and changing agendas in Congress and the executive branch. Thus, funding for the agency often bears little relation to the mandates and missions assigned by Congress. The most elegant and detailed schemes envisioned when a statute is written can become unworkable when resources

drugs than of prescription Class II devices. The disjointed evolution of two regulatory schemes governing medical technologies can lead to public misunderstanding and confusion over the FDA's powers and responsibilities.

are inadequate. Necessary improvisation and tough choices at the FDA between competing priorities can move the regulatory regime in unforeseen directions.

The last force affecting the history of medical-device regulation is the inherent difficulty of resolving some core issues, which can cause them to arise again and again as different solutions prove unsatisfactory. That those issues have recurred throughout the 35 years since the medical-device statute's enactment in 1976 demonstrates how difficult they are to resolve. Those issues include

- Whether the 510(k) mechanism as originally enacted in 1976 or even as modified in 1990 or 1997 can even theoretically provide determinations about the safety and effectiveness of each product reviewed. Simply stated, must a finding that a new device is substantially equivalent to another lawfully marketed product (the predicate device) necessarily be a determination that the new device is safe and effective?
- Whether the FDA can reasonably ensure the quality and consistency of 510(k) clearance decisions. Manufacturers desire predictability of the regulatory process to manage what they maintain is the inherent uncertainty and risk in innovation. Moreover, because the FFDCRA requires the FDA to accept any marketed device as a predicate, flawed 510(k) decisions become embedded and must be perpetuated.
- Whether the FDA has appropriately used its authority to establish performance standards or special controls over Class II devices. What does it mean for public health if the “reasonable assurance of the safety and effectiveness” of a Class II device cannot, by definition, be ensured by general controls alone but the agency does not impose any additional controls? Is the adoption of special controls mandatory or discretionary?
- Whether the procedural requirements imposed by law properly balance the interests of private parties with the need for efficient and effective government actions. The preliminary recommendations of the Center for Devices and Radiological Health (CDRH) 510(k) Working Group asserted that “CDRH’s postmarket tools, while valuable, have important limitations” (FDA, 2010, p. 4). When powers given to the FDA are so encumbered by “due process” demands that they become unworkable and are not used, no one is served.
- Whether lack of safety or effectiveness of marketed products can be promptly identified and addressed. Ultimately, the regulatory scheme to safeguard public health can be considered reliable only if society can be confident that consumers are being protected. The most important element in gaining that knowledge is surveillance of adverse

medical experiences. Without a robust surveillance network to detect injuries and product ineffectiveness, there is no basis for judging the system. The absence of data on a problem does not demonstrate that a problem does not exist.

- Whether the appropriate balance has been achieved between premarket clearance (the gatekeeping function) and postmarketing controls. Premarket clearance may add little value to protecting the public (while inhibiting innovation); in 1997, Congress eliminated 510(k) notification requirements for most Class I devices. But the preliminary recommendations of the CDRH 510(k) Working Group stated that “CDRH’s postmarket tools, while valuable, have important limitations and are not sufficient to serve as a substitute for a high-quality premarket review” (FDA, 2010, p. 4). The Working Group seems to have concluded that inadequate or ineffective postmarketing controls justify increased rigor in the preclearance process to protect consumers.

This appendix seeks to provide a chronologic inventory of medical-device legislation and external studies of its implementation. It is regrettably sprawling, shifting back and forth over seemingly disparate events and describing laws as originally enacted, even though they have been superseded by amendments. Readers are encouraged to keep in mind the six issues just identified so that they can understand the relevance of the materials presented here and to accept our apologies for the somewhat disjointed structure adopted. Although the FDA has undertaken many internal reviews and efforts to improve the process, this appendix draws most of its information from congressional materials. The focus here is on what Congress has perceived and has done concerning the goals and implementation of the FDA’s regulation of medical devices.

DEVICE REGULATION UNDER THE 1938 FEDERAL FOOD, DRUG, AND COSMETIC ACT

The Pure Food and Drug Act of 1906 did not cover medical devices. As Congress approached overhaul of the statute in the 1930s, it added that class of product to FDA jurisdiction. For all intents and purposes, however, government authority and industry legal requirements in the draft legislation were identical for both drugs and devices. Until the brink of enactment, the bills imposed no premarket review of either but subjected them to prohibitions against being “adulterated” or “misbranded.” Those terms were legal words of art and covered a variety of specific mandates or prohibitions. For example, a drug or device would be “adulterated” if it had been prepared under insanitary conditions whereby the product *may* have been rendered

injurious to health. A medical product would be “misbranded” if its label failed to identify the name and address of the manufacturer or distributor.⁴

The draft statute further provided that once the FDA discovered a violation of the requirements, it could seize the noncompliant product, seek an injunction against its manufacturer or distributor to prevent future violations, or recommend to the Department of Justice criminal prosecution of the persons responsible.⁵ Those three options were the only enforcement tools in the bill.

Final legislative action was precipitated by the elixir sulfanilamide disaster, which involved a product that put an effective drug (sulfa) into solution with a toxic solvent (diethylene glycol) that caused upward of 100 deaths in the winter of 1937–1938 (Carpenter, 2010, pp. 85–108). In response, Congress added a distinct provision applicable only to “new drugs”: premarket review of a new drug application (NDA) for safety. The manufacturer was not required to obtain FDA approval but only to provide the agency 60 days in which to make a safety assessment. If the government failed to find any safety issues within the 60-day window, the drug could enter the market.⁶

In that form, the FFDCA became law in 1938.

Over the next several decades, the FDA directed much of its enforcement efforts to devices, using the adulteration and misbranding provisions of the FFDCA to deal with grossly hazardous or fraudulent products. By the early 1960s, however, the agency’s attention was drawn to new technologies that were being introduced without premarket clinical testing, quality control, or patient consent.⁷ In 1962, Congress amended the new drug provisions of the FFDCA to require affirmative FDA approval of an NDA before marketing could begin and to require that a new drug be shown to be effective as well as safe.⁸

The broadened premarket authority for “new drugs” encouraged the FDA to consider applying these powers to medical devices. The opportunity to do so was supplied by the overlap in the definitions of *drug* and *device* in the original 1938 Act. As written, the terms had similar scope and were differentiated only by a drug’s being an “article” whereas a device was an “instrument, apparatus, . . . [or] contrivance” that was either recognized in an official compendium, such as the US Pharmacopeia; was “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease”;

⁴FFDCA, Pub. L. No. 75-717, §§ 501-02, 52 Stat. 1040, 1049-50 (1938).

⁵FFDCA §§ 301-04, 52 Stat. at 1042-45.

⁶FFDCA § 505, 52 Stat. at 1052-53.

⁷H.R. REP. NO. 94-853, at 7-8 (1976) (House Report on the Medical Device Amendments of 1976).

⁸Drug Amendments of 1962, Pub. L. No. 87-781 (codified as amended at 21 USC § 355(b)(1)(a)(A)).

or was “intended to affect the structure or any function of the body.”⁹ In two important legal cases, the FDA persuaded federal courts that it had statutory authority to declare that products that were generally thought of as medical devices were drugs and new drugs requiring agency approval of an NDA before marketing. One product consisted of a disposable applicator, a nylon ligature loop, and a nylon locking disk used to tie off severed blood vessels during surgery; the disk and at least some of the nylon thread remained in the patient’s body.¹⁰ The other product was an antibiotic-sensitivity disk.¹¹ Ultimately, the FDA classified a number of products as drugs before the Medical Device Amendments were enacted, including contact lenses, injectable silicone, pregnancy-test kits, and bone cement (Hutt et al., 2007, p. 977). Only devices classified as drugs were subject to any premarket review by the FDA before 1976.

DEVELOPMENT AND ENACTMENT OF THE MEDICAL DEVICE AMENDMENTS OF 1976

Presidents Kennedy, Johnson, and Nixon all recognized “the need for more comprehensive authority to regulate medical devices.”¹² At the direction of the secretary of the Department of Health, Education, and Welfare (now the Department of Health and Human Services), Theodore Cooper, director of the National Heart and Lung Institute (now the National Heart, Lung, and Blood Institute) chaired a study group to consider how to approach new legislation; the group issued its report in September 1970. Among its recommendations were better differentiation of devices and drugs in federal law with the adoption of a new and distinct regulatory regime for medical devices, preclearance review of some devices with the extent of premarket review depending on the novelty and potential hazards of the devices, and expansion of the FDA’s nonpreclearance authority over medical devices. The last category included mandatory records and reports, adherence to good manufacturing practices, manufacturer registration, and FDA inspection of factories.¹³

Over the next few years, several high-profile public-health problems that involved medical devices were observed. Among the most publicized was the Dalkon Shield, an intrauterine contraceptive device (IUD) that was introduced into the market in late 1970. By 1975, at least 16 deaths, 25 miscarriages, numerous cases of pelvic perforation and pelvic infection, re-

⁹FFDCA § 201(g)-(h), 52 Stat. at 1041 (1938).

¹⁰AMP, Inc. v. Gardner, 389 F.2d 825 (2d Cir. 1968), cert. denied, 393 U.S. 825 (1968).

¹¹U.S. v. An Article of Drug . . . Bacto-Unidisk, 394 U.S. 784 (1969).

¹²H.R. REP. NO. 94-853, at 9.

¹³H.R. REP. NO. 94-853, at 9-10; U.S. DEP’T OF HEALTH, EDUC., & WELFARE, MEDICAL DEVICES: A LEGISLATIVE PLAN *passim* (1970) (Cooper Committee Report).

removal of the IUD for medical reasons, and pregnancies due to IUD failure had been reported. Marketing of the device ceased by 1976. Other examples cited by the House of Representatives committee responsible for the 1976 legislation included pacemaker failures and dangerous eye infections after implantation of intraocular lenses.¹⁴

In 1974 and 1975, the Senate passed comprehensive legislation for the regulation of medical devices.¹⁵ The House of Representatives, however, did not move with its own bill until March 1976.¹⁶ A conference committee reconciled the differences between the two bills.¹⁷ The Medical Device Amendments of 1976 (MDA) passed both houses of Congress and were signed into law by President Ford on May 28.¹⁸

As discussed below, the medical-device law has since been amended many times, most significantly in 1990, 1992, 1997, 2002, 2004, 2005, and 2007. None of those amendments, however, has altered the fundamental regulatory regime established in 1976.

BASIC STRUCTURE OF THE MEDICAL DEVICE AMENDMENTS

Although the new statute provided for premarket review of some products, protection of public health rested predominantly on rules enforced by the FDA after a product entered the market. In that respect, the MDA departed from the approach taken for drugs in 1962, which put extraordinary emphasis on the FDA premarket approval process as the primary means of protecting consumers. For devices, the “gatekeeper” function of premarket approval provided an additional layer of protection but only for a small array of products (Class III), and it did not replace or render unnecessary the variety of other requirements applicable to all other devices. As originally enacted, the 510(k) clearance process was not intended to be a major preclearance mechanism.

Distinguishing Devices from Drugs

To establish a distinctive regulatory scheme for medical devices, Congress first had to address the overlapping definitions of *drug* and *device* in the 1938 law. As noted above, federal courts found the terms sufficiently congruent to uphold the FDA's determination that several products thought

¹⁴H.R. REP. NO. 94-853, at 8 (1976).

¹⁵S. REP. NO. 94-33, at 1 (1975) (accompanying S. 510).

¹⁶H.R. REP. NO. 94-853, at 1 (accompanying H.R. 11124).

¹⁷H.R. REP. NO. 94-1090, at 1 (accompanying S. 510).

¹⁸Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (hereinafter 1976 MDA).

of as devices could nevertheless be regulated as drugs. The MDA provided as follows

The term “device” . . . means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

1. recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure of any function of the body of man or other animals,

and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes.¹⁹

General Controls

The MDA established requirements for industry and authorities for the FDA that would apply to all medical devices. Those provisions are usually described as the general controls and include the following:²⁰

- Applying to all devices the “adulteration” provisions of the 1938 Act, including—
 - prohibiting potential or actual contamination of the product;²¹ and
 - requiring adherence to good manufacturing practice regulations promulgated by the FDA.²²
- Applying to all devices the “misbranding” provisions of the 1938 Act, including—
 - prohibiting any false or misleading statements in labeling,²³

¹⁹FFDCA § 201(h), 90 Stat. 575 (1976). The definition was changed in 1992 to substitute “its primary intended purposes” for “any of its principal intended purposes.” 106 Stat. 240 (1992). For current definition see FFDCA § 201 (h), 21 USC § 321(h) (2006).

²⁰This summary necessarily abbreviates the statutory language. It is intended to give an overview, not provide a detailed description of each provision of the law.

²¹FFDCA § 501(a)(1), (a)(2)(A), (3), (4)(A), 21 USC § 351(a)(1), (a)(2)(A), (3), (4)(A) (2006).

²²FFDCA §§ 501(h), 520(f), 21 USC §§ 351(h), 360j(f) (2006).

²³FFDCA § 502(a), 21 USC § 352(a) (2006).

- o requiring disclosure of the name and address of the manufacturer,²⁴ and
- o mandating “adequate directions for use” and “adequate” warnings against unsafe use in labeling for the product.²⁵
- Authorizing the FDA to restrict the sale, distribution, or use of a device (a) only on the authorization of a licensed practitioner or (b) upon such other conditions as the FDA may prescribe, if—because of the potential for harm or the collateral measures necessary to its use—the FDA determines that there cannot otherwise be reasonable assurance of the safety and effectiveness of the device (devices so designated are called “restricted devices”).²⁶
- Prohibiting false or misleading advertising of a “restricted device.”²⁷
- Mandating disclosures in all advertising for “restricted devices” of a brief statement of intended uses and relevant warnings.²⁸
- Requiring registration with the FDA by all manufacturers of medical devices.²⁹
- Mandating listing with the FDA by a registered firm of all devices it currently markets.³⁰
- Requiring notification to the FDA of any new device proposed to be marketed by a registered firm, at least 90 days prior to introduction for commercial distribution [this is the provision that gave rise to the 510(k) process that is the focus of the committee’s study].³¹
- Authorizing the FDA to inspect factories in which medical devices are manufactured and to inspect records relating to “restricted devices” in those facilities.³²
- Authorizing the FDA to ban a device from sale or use if it presents substantial deception or an unreasonable and substantial risk of illness or injury.³³
- Authorizing the FDA to order notification to physicians and others (including patients and other end users) if three conditions are all met: (a) a device presents an unreasonable risk of substantial harm to the public health, (b) notice is necessary to eliminate the risk, and (c) no other more practicable means is available to eliminate this risk.³⁴

²⁴FFDCA § 502(b), 21 USC § 352(b) (2006).

²⁵FFDCA § 502(f), 21 USC § 352(f) (2006).

²⁶FFDCA § 520(e), 21 USC § 352(e) (2006).

²⁷FFDCA § 502(q), 21 USC § 352(q) (2006).

²⁸FFDCA § 502(r), 21 USC § 352(r) (2006).

²⁹FFDCA § 510(c), 21 USC § 352(c) (2006).

³⁰FFDCA § 510(j)(1), 21 USC § 360(j)(1) (2006).

³¹FFDCA § 510(k), 21 USC § 360(k) (2006).

³²FFDCA § 704(a), 21 USC § 374(a) (2006) (2006).

³³FFDCA § 516, 21 USC § 360f (2006).

³⁴FFDCA § 518(a), 21 USC § 360h(a) (2006).

- Authorizing the FDA to order a manufacturer to repair a device, replace the device, and/or refund the purchase price of the device, if four conditions are all met: (a) the device presents an unreasonable risk of substantial harm to the public health, (b) the device was not properly designed or manufactured to the state of the art when designed or made, (c) the unreasonable risk was not caused by someone other than the manufacturer to exercise due care with the installation, maintenance, or use of the device, and (d) notification by itself would not be sufficient to eliminate the unreasonable risk, so that repair, replacement, and/or refund by the manufacturer is necessary to eliminate this risk.³⁵
- Authorizing the FDA to require manufacturers to maintain records and submit reports (such as reports of adverse medical events associated with medical devices) to assure that a device is not adulterated or misbranded and to otherwise assure its safety and effectiveness³⁶ (the statute presumed, however, that Class I devices would not be subject to reporting in ordinary circumstances).³⁷
- Authorizing the FDA to order detention of a device for up to 20 days, if the agency believes it is adulterated or misbranded, to permit the preparation and filing of a court action for seizure of the product.³⁸

It must be emphasized that the foregoing requirements and authorities were established in 1976 almost always without regard to the assignment of a medical device into Class I, Class II, or Class III (the classes are defined below). The law has since been amended to exempt many Class I products from some general controls or to limit the application of general controls to subsets of Class II or III products that pose higher risks. But the original MDA rarely made those distinctions. In cases in which authority was conditioned on an FDA finding of a higher degree of risk, the finding was to be made without regard to the prior classification of the device.

Device Classification and Premarket Review

The 1976 act adopted a three-tier system to determine the need for *additional* regulatory controls in the form of premarket review to protect and promote public health. The tiers correspond to the perceived risks posed by the devices. Thus, the law represented a sharp break with the approach

³⁵FFDCA § 518(b), 21 USC § 360h(b) (2006).

³⁶FFDCA § 519(a), 21 USC § 360i(a) (2006).

³⁷FFDCA § 519(a)(8), 21 USC § 360i(a)(8) (2006) (redesignated from 519(a)(5) by the Medical Device Amendments of 1992, Pub. L. No. 102-300, § 5(a)(1), 106 Stat. 238, 239 (1992) (hereinafter 1992 MDA).

³⁸FFDCA § 304(g), 21 USC § 334(g) (2006).

taken with respect to pharmaceutical agents, for which a uniform and rigorous system was established for all new agents and an only slightly less demanding and uniform system for generic copies of these agents. Because of the wide variety among devices, Congress recognized that uniformity was neither necessary nor ideal to attain the ultimate public-health goal of a “reasonable assurance of the safety and effectiveness” of each marketed device.

Congress directed that the safety and effectiveness of a device be determined with respect to the persons for whose use the device is intended, with respect to the conditions of use in the labeling of the device, and by “weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.”³⁹

A Class I device is one for which the general control requirements and any special control authorities that the FDA chooses to exercise with respect to the device would be sufficient to provide reasonable assurance of safety and effectiveness. Class I could also include any device on which there is insufficient information to judge the adequacy of general controls but that is not represented to be for use in supporting or sustaining human life (or preventing impairment to health) and does not present an unreasonable risk of illness or injury.⁴⁰

A Class II device is one that cannot be classified into Class I (because the general controls are not sufficient by themselves to provide reasonable assurance of safety and effectiveness) but on which there is sufficient information to establish a performance standard or other special controls to provide reasonable assurance.⁴¹ A performance standard might include provisions regarding the construction, components, ingredients, and properties of the device and its comparability with power systems; provisions for the testing of the device to ensure conformity to the standard; provisions for measurement of performance characteristics of the device; provisions making the device a “restricted device”; and special labeling requirements related to the installation, maintenance, operation, and use of the device.⁴² The statute was ambiguous as to whether performance standards were required (that is, necessary to provide reasonable assurance of safety and effectiveness that could not be provided by general controls alone) or discretionary. In the separate section setting forth the procedures for promulgation of performance standards, the MDA stated that the FDA “may” establish performance standards but did not mandate them for Class II devices.⁴³ If general controls were by definition inadequate, the absence of performance

³⁹FFDCA § 513(a)(2), 21 USC § 360c(a)(2) (2006).

⁴⁰FFDCA § 513(a)(1)(A), 21 USC § 360c(a)(1)(A) (2006).

⁴¹FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

⁴²FFDCA § 514(a)(2), 21 USC § 360d(a)(2) (2006).

⁴³FFDCA § 514(a)(1), 21 USC § 360d(a)(1) (2006).

standards must have meant that the safety and effectiveness of a Class II device could not be reasonably assured.

A Class III device is one that is represented for use in supporting or sustaining life (or for substantial use in preventing impairment of health) or that creates a potential unreasonable risk of illness or injury but that cannot be classified into Class I (because the general controls are inadequate to give reasonable assurance of safety and effectiveness) or Class II (because there is not sufficient information to determine that additional special controls would be sufficient to provide the requisite assurance).⁴⁴

The MDA directed the FDA to classify all then-marketed medical devices (so-called preamendment devices) into one of the three classes on the basis of the criteria just outlined.⁴⁵ The 1976 Amendments also provided mechanisms for the FDA to reclassify devices originally placed in Class III into lower classes when premarket review was no longer needed to ensure the safety and effectiveness of the device type.⁴⁶ In addition, the MDA provided that devices that were not on the market when the bill became law (so-called postamendment devices) would be automatically placed in Class III—at least until reclassified.⁴⁷

Classification governed the type and extent of FDA review before a product could enter the market. Class III devices were subject to the most intense scrutiny.

For Class III devices, Congress required affirmative FDA approval before marketing.⁴⁸ An application for PMA must contain the following major elements: full reports of all information, known or reasonably known to the applicant, regarding investigations to assess the safety and effectiveness of the device (including clinical investigations of safety and effectiveness); a full statement of the components and properties of the device and of the principles of its operations; a full description of the methods used in and facilities and controls used for its manufacture, processing, and (when relevant) packaging and installation; specimens of the labeling proposed to be used for the device; and any other information relevant to the PMA that the FDA (with the concurrence of an advisory panel) may require.⁴⁹ The 1976 statute did not provide the FDA any explicit authority to waive those requirements. The agency was given 180 days to review a PMA and grant or deny its approval.⁵⁰ During the review process, the FDA could on

⁴⁴FFDCA § 513(a)(1)(C), 21 USC § 360c(a)(1)(C) (2006).

⁴⁵FFDCA § 513(b)–(d), 21 USC § 360c(b)–(d) (2006).

⁴⁶FFDCA § 513(e), 21 USC § 360c(e) (2006).

⁴⁷FFDCA § 513(f)(1), 21 USC § 360c(f)(1) (2006).

⁴⁸FFDCA §§ 513(a)(1)(C), 515(a), 515(a), 21 USC §§ 360c(a)(1)(C), 360e(a) (2006).

⁴⁹FFDCA § 515(c), 21 USC § 360e(c) (2006); see 21 CFR § 814.20 for the FDA's regulations detailing the required format and contents of a PMA.

⁵⁰FFDCA § 515(d)(1), 21 USC § 360e(d)(1) (2006).

its own initiative (and, on request of an applicant, would have to) refer the PMA to an outside advisory panel, which would report its conclusions and recommendations.⁵¹ Grounds for denial include the lack of showing of a reasonable assurance of either safety or effectiveness, noncompliance with good manufacturing practices, or false or misleading labeling.⁵² The FDA could condition approval on compliance with one or more of a variety of postapproval requirements, including the completion of studies to confirm the safety, effectiveness, and reliability of the device for its intended use.⁵³ Once a PMA was approved, the applicant had to obtain additional FDA approvals before making changes in the labeling of the device, its indications for use, its packaging or sterilization procedures, the performance or design specifications, its components, principles of operation, physical layout, or method of manufacture.⁵⁴

For Class I devices, the 1976 law contemplated that the sponsor of a new product that was classified in Class I would submit a notice to the FDA at least 90 days before marketing; the notice would set forth the simple fact that the device was so classified. That notice became known as a 510(k) notification after the section of the MDA that required a manufacturer to notify the FDA of a new product before marketing it.⁵⁵ If the agency concurred or failed to respond within 90 days, the product could enter the market; otherwise, the sponsor was notified that the product could not enter the market without further action being taken (for example, approval of a PMA).

For premarket review of a Class II device, the 1976 law seemed to contemplate that the sponsor of a new product would submit to the FDA a notice under Section 510(k) setting forth the fact that the device was classified in Class II and, if a performance standard had been promulgated, appropriate certification or evidence that the product conformed to the standard.⁵⁶ Again, the FDA would review the notice and determine whether it agreed.

The classification of preamendment devices did not include any evaluation of the safety or effectiveness of the individual medical devices. The FDA created advisory panels to assist in the device classification process. These panels reviewed information on the risks posed by types of devices, including the potential risks resulting from a failure of lack of effectiveness, and recommended into which class the device type should be placed, in order to provide a reasonable assurance of safety and effectiveness. Neither the panels nor the FDA itself undertook an assessment of the clinical safety or

⁵¹21 CFR § 814.44(a), (b).

⁵²FFDCA § 515(d)(2), 21 USC § 360e(d)(2) (2006).

⁵³21 CFR § 814.82.

⁵⁴FFDCA § 515(d)(6), 21 USC § 360e(d)(6) (2006); limited exceptions are provided in 21 CFR § 820.39(d).

⁵⁵FFDCA § 510(k), 21 USC § 360(k) (2006).

⁵⁶FFDCA § 510(k), 21 USC § 360(k); § 514(a)(1)(B), 21 USC § 360d(a)(1)(B).

effectiveness of individual devices during the original classification process. Once a device type was assigned to Class III, the statute directed the FDA to promulgate a regulation calling for manufacturers of devices of that type to submit a PMA application. The agency would then (and only then) undertake a review of the safety and effectiveness of the specific devices. For device types placed into Class I or Class II, there was no mechanism for the systematic post-classification review of safety and effectiveness. Congress envisioned instead that the agency would use its postmarketing tools to identify and address issues of lack of safety or lack of effectiveness case by case.

In short, device classification was established in the MDA primarily in relation to premarket review. Class I devices needed no additional review once a device's status as Class I was confirmed; the general controls were sufficient to protect public health. Class II devices needed only limited supplemental review to verify conformity with any established performance standard. Class III devices, the truly novel devices that presented significant risks to health, were the only ones that Congress wanted to undergo premarket FDA scrutiny similar to that of new drugs.⁵⁷

Transition Problems

Congress wanted the new standards of safety and effectiveness to be applied to the Class III devices that were already in the marketplace in 1976. Whenever Congress requires such a retrospective review of existing products, however, it faces a series of challenges:

- Should the law permit continued marketing of the existing products while they are undergoing the new review? Immediate suspension would disrupt routine activities; in the case of medical products, it would deny healthcare professionals and patients access to previously available technologies.
- If existing products can continue to be marketed, should the law also permit new products that are identical (or nearly so) to be launched before the review of the existing products has been completed? On one hand, introduction of new products can proliferate the use of the technology before it has been assessed. On the other hand, giving the existing products a monopoly (by excluding competitors until completion of the retrospective review) is unfair to newcomers and creates perverse incentives for the incumbent manufacturers to slow the review process.

⁵⁷By 1976, the FDA was asserting that virtually all prescription drug products were considered to be new drugs, including all those which had entered the market after 1938, even if they entered without approval of an NDA (such as generic versions of previously approved drugs). See Vodra, 1981.

- If marketing is permitted to continue during the transition period, should the law impose a deadline for completion of the review? Without a deadline, the temporary exception could become a permanent grandfather clause under which the existing products (and equivalent newcomers if permitted) are exempt from the review process indefinitely—perhaps until the products become obsolete. Moreover, without a deadline, manufacturers of products that might not pass the review have a strong interest in prolonging the transition for as long as possible.

In three prior amendments to the 1938 FFDCA, when Congress required a retrospective review of products on the market at the time of the amendments, Congress had taken similar approaches to those issues. In all cases, existing products had been allowed to remain in the market during review of the new products, and competitors were allowed to enter the market before completion of review and retroactive application of new regulatory standards. The earlier amendments tried different approaches to ensure that the review was completed with reasonable dispatch, but none was fully successful. In every case, the statutory deadline was not met (IOM, 2010, pp. 3–6).

In the MDA, Congress directed the FDA to promulgate regulations for each type of Class III device that would require approval of a PMA. The issuance of the individual regulations was to follow a timetable established by the FDA. In the meantime, however, the preamendment products could remain on the market pending the promulgation of the regulation calling for the PMA and its submission and review.⁵⁸ During the transition period for each type of Class III device, new (postamendment) products of the same type would also be permitted to enter the marketplace.⁵⁹ But the manufacturer of a postamendment device would not have to submit and obtain approval of a PMA before the manufacturers of the preamendment were required to. Instead, the manufacturer would submit a 510(k) notification demonstrating that its proposed product was “substantially equivalent” to a Class III preamendment device. Once PMA requirements were imposed, however, the use of the 510(k) would terminate. The 510(k) notification process was a purely transitional tool for Class III devices, which would end as the PMA requirements were fully implemented.

Another part of the 1976 amendments provided that all postamendment devices were automatically to be classified into Class III with specific exceptions.⁶⁰ The primary exception involved a postamendment device that was substantially equivalent to another device of the same type that either was

⁵⁸FFDCA § 515(b)(1), 21 USC § 360e(b)(1) (2006).

⁵⁹FFDCA § 513(f)(4), 21 USC § 360c(f)(4) (2006).

⁶⁰FFDCA § 513(f)(1), 21 USC § 360c(f)(1) (2006).

a preamendment device that had not been classified into any class or was not a preamendment device but had already been classified into Class I or Class II.⁶¹ The FDA permitted manufacturers of postamendment devices to demonstrate substantial equivalence to a preamendment device in Class I or II as part of the 510(k) submission. An alternative exception provided that the postamendment device would not be in Class III if the FDA, in response to a petition, classified it into Class I or Class II.⁶²

Congress assumed that ultimately postamendment devices would also be classified, on the basis of risk, into the appropriate category. But until then, any new product proposed for marketing after 1976 would be subject to PMA requirements unless it was substantially equivalent to a preamendment device already in Class I or Class II (or not yet classified) or was reclassified by the FDA down from Class III. That particular provision could place enormous resource demands on the agency as technology evolved and newer devices were developed. The FDA might have to either process increasing numbers of PMAs or reclassify the new devices into Class I or II through a procedurally cumbersome, labor-intensive, and time-consuming process.

There was another pathway: The agency might determine that the proposed new device was substantially equivalent to a device classified in Class I or II, notwithstanding the changes in technology, and permit it to be marketed pursuant to a 510(k) notification.

Definition of Substantial Equivalence

Congress did not define *substantial equivalence* in the legislation, but the House committee report contained the following statement:

The term “substantially equivalent” is not intended to be so narrow as to refer only to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The Committee believes that the term should be construed narrowly where necessary to assure the safety and effectiveness of a device but not so narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness. Thus, differences between “new” and marketed devices in materials, design, or energy source, for example, would have a bearing on the adequacy of information as to a new device’s safety and effectiveness, and such devices should be automatically classified into class III. On the other hand, copies of devices marketed prior to enactment, or devices whose variations are immaterial to safety and effectiveness would not necessarily fall under the automatic classification scheme.⁶³

⁶¹FFDCA § 513(f)(1)(A), 21 USC § 360c(f)(1)(A) (2006).

⁶²FFDCA § 513(f)(1)(B), 21 USC § 360c(f)(1)(B) (2006).

⁶³H.R. REP. NO. 94-853, at 36-37.

The MDA did not spell out the required contents of a 510(k). Generally, however, a 510(k) would not have to contain a description of the components and properties of a device, the principles of its operations, the methods of manufacture, or specimens of the labeling proposed to be used for the device. It need only set forth its proposed intended use or indications for use, the device to which substantial equivalence is claimed, and evidence demonstrating that equivalence.

IMPLEMENTATION OF THE MEDICAL DEVICE AMENDMENTS: LONG-TERM TRENDS

Resource Limitations

Two overarching factors have affected the FDA's efforts to carry out the MDA. First, the agency never had sufficient resources to fulfill all the congressional directives for medical-device classification and regulation. Although a continuous and consistent dataset of funding and staffing from FY 1976 to FY 2010 is not available, there are snapshots. The information that follows compares "apples, oranges, and other fruit" and can be viewed only as an approximation of the resources over time.

In FY 1981, FY 1982, and FY 1983, the numbers of full-time equivalent (FTE) staff-years for the Bureau of Medical Devices and the Bureau of Radiological Health—which were merged in 1982 to form the National Center for Devices and Radiological Health, which is now CDRH—were 836, 786, and 779, respectively (GAO, p. 1983, 4). From 1982 to 1987, CDRH underwent a 5% staff reduction.⁶⁴ In 1989, GAO reported that the FDA budget for FY 1990 would provide the agency with 430 FTE positions *fewer* than it had in FY 1980, a 5.5% reduction (GAO, 1989a, p. 12).

Later data are more detailed. Between FY 1990 and FY 1994, the numbers of FTEs assigned to the 510(k) program were 120, 131, 126, and 140 (GAO, 1996, p. 35). From FY 1991 to FY 1994, the median time required by the FDA to complete 510(k) reviews increased from an average of just under 90 days to more than 160 days, then up to 230 days, and finally down to 152 days, all well beyond the 90-day goal of the law (GAO, 1995, pp. 5–6). In the next 2 fiscal years, FY 1995 and FY 1996, the number of FTEs assigned to the 510(k) program rose to 186 and 211, respectively—a 50% increase in just 2 years (GAO, 1996, p. 35). In those 2 fiscal years, the median 510(k) review time fell back to about 90 days (GAO, 1997b, p. 4).

A 2009 GAO report described the total staffing resources for the devices

⁶⁴*Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't. of the H. Comm. on Energy and Commerce*, 100th Cong. 387 (1987) (statement of James S. Benson, Deputy Director, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services).

program from FY 1999 to FY 2008. The number fluctuated around 1,500, with a low of 1,454 (FY 2002) and a high of 1,564 (FY 2008) (GAO, 2009a, p. 42). For premarket review within CDRH, including both 510(k) submissions and PMA applications, the number of FTEs increased in FY 2004–FY 2008 from 516 to 618.⁶⁵ Thus, it appears that only in the past few years, with the adoption of user fees, have the resources committed to premarket reviews increased substantially.

Procedural Demands

The second fundamental factor affecting implementation was an increase in procedural steps needed for the FDA to take administrative actions.

Soon after taking office, President Reagan issued Executive Order 12291 on *Federal Regulations* to implement new controls over the issuance of regulations by all US agencies.⁶⁶ It specified that agencies must have “adequate information concerning the need for and consequences of proposed government action” and must prepare a regulatory impact analysis for any major rule or regulation that could affect the economy, increase costs or prices, or substantially and adversely affect competition, productivity, or innovation. Moreover, regulatory action was permitted only if the potential benefits to society outweighed the potential costs, if the proposed action maximized the new benefits, and if alternative approaches had been considered to achieve the same objective at a lower net cost to society. To enforce those standards, OMB was required to review all proposed and all final major regulations before publication by an agency. The effect of the new controls was to increase the time and administrative burdens on the FDA to draft and issue regulations. The executive order is still in effect.

Soon after the issuance of Executive Order 12291, HHS Secretary Richard Schweiker issued an order that modified the delegation of authority to the commissioner of food and drugs to promulgate regulations implementing the FFDCAs. The order reserved the secretary’s authority to approve the FDA regulations that addressed important public issues involving quality, availability, marketability, or cost of FDA-regulated products.⁶⁷ This order is still in effect.

The MDA dictated that many agency actions be carried out only through proceedings involving the issuance of regulations or analogous procedures for soliciting public input and establishing final orders, for example, to classify or reclassify devices,⁶⁸ to establish performance standards

⁶⁵*Id.* at 50.

⁶⁶Exec. Order No. 12291, 46 Fed. Reg. 13,193 (Feb. 17, 1981).

⁶⁷46 Fed. Reg. 26,052 (May 11, 1981) (2006).

⁶⁸FFDCA § 513(c)–(f), 21 USC § 360c(c)–(f) (2006).

for specific types of Class II devices,⁶⁹ to require PMAs for specific types of preamendment Class III devices,⁷⁰ to ban devices,⁷¹ to require records and reports from manufacturers,⁷² to restrict the sale or use of an individual device to medical practitioners,⁷³ and to specify good manufacturing practices for manufacturers.⁷⁴

The MDA's requirements for promulgation of regulations often went beyond the basic requirements of the Administrative Procedure Act, which governs the promulgation of federal regulations generally. For performance standards for Class II devices, for instance, the MDA required that five separate notices be published in the *Federal Register*: a notice initiating proceedings to establish a performance standard, which provided manufacturers an opportunity to request a change in classification in lieu of a standard; a notice inviting submission of existing voluntary or industry standards as a proposed FDA standard and offers to develop the standard; a notice accepting or rejecting offers and announcing a decision to proceed with a standard; a notice proposing a standard and inviting comments; and a notice promulgating the final standard.⁷⁵ If it were requested by a manufacturer, the FDA had to convene an advisory committee to review the proposed standard before issuing a final order.⁷⁶ In the wake of Executive Order 12291, the FDA also decided that before it would initiate a proceeding to establish a performance standard, it would consider the following alternative steps: requesting that manufacturers voluntarily solve device problems, publicizing particular device problems, publishing educational and technical information, participating in developing a voluntary standard, using other general controls, and developing guidelines.⁷⁷ It should surprise no one, therefore, that the FDA did not promulgate a single Class II performance standard in the period 1976–1990 and has adopted very few since.

The effect of those procedural burdens is also illustrated by the FDA's implementation of the MDA's restricted-device provision. Congress empowered the agency to issue regulations imposing restrictions on the sale,

⁶⁹1976 MDA § 514 (b)–(e) (removed by the Safe Medical Devices Act of 1990, Pub. L. No. 101-629 § 6(a)(2), 104 Stat. 4511, 4519-20 (1990) [hereinafter SMDA]).

⁷⁰FFDCA § 515(b), 21 USC § 360e(b) (2006).

⁷¹FFDCA § 516(a), 21 USC § 360f(a) (2006).

⁷²FFDCA § 519(a), 21 USC § 360i(a) (2006).

⁷³FFDCA § 520(e), 21 USC § 360j(e) (2006).

⁷⁴FFDCA § 520(g), 21 USC § 360j(g) (2006).

⁷⁵1976 MDA § 514 (b)–(g), 90 Stat. 539 (Subsections (b)–(f) were removed by SMDA § 6(a)(2); Subsection (g) is now codified as 21 USC § 360d(b) (2006)).

⁷⁶1976 MDA § 514(g)(5) (now codified as 21 USC § 360d(b)(5) (2006)).

⁷⁷FDA Bureau of Medical Devices, Policy for Class II Medical Devices (August 1982) (unpublished internal draft, cited in OFFICE OF TECH. ASSESSMENT, CONGRESS OF THE UNITED STATES, FEDERAL POLICIES AND THE MEDICAL DEVICES INDUSTRY 109-110, 250 n. 387 (1984)).

distribution, or use of a device.⁷⁸ Once a device was declared restricted, the FDA was authorized to regulate its advertising and promotion and to inspect its manufacturing records.⁷⁹ Before the MDA's enactment, many devices were marketed as "prescription devices" that could be sold only to or on order of or used only by a physician. One week after President Ford signed the bill into law, the FDA published a notice in the *Federal Register* declaring that existing prescription devices were now "restricted devices."⁸⁰ Several device manufacturers challenged the FDA's legal position, and federal courts ruled that the FDA had to use formal notice-and-comment rule-making to declare devices restricted.⁸¹ In response, the FDA proposed a rule on restricted devices in October 1980, observing that the decision of whether a device was a prescription device was often made by individual manufacturers without consistent standards or objective criteria.⁸² A year later, however, the FDA withdrew the proposed rule, stating that comments argued that the existing system for designating devices as prescription-only devices was adequate and that Executive Order 12291 directed the FDA not to impose new requirements unless the benefits outweighed the costs.⁸³ The agency went on to say that it would rely on its other authorities, such as its power to inspect records that were required to be kept under the good-manufacturing-practice regulations and under the dispensing and labeling requirements for prescription and nonprescription devices. The FDA has not attempted since 1981 to issue regulations under the MDA's restricted-device provision although it has used its authority to designate individual devices as restricted in conjunction with PMA approvals⁸⁴ and with special controls on some Class II devices.⁸⁵

Effects of Resource and Process Constraints

The consequences of inadequate resources and elaborate procedural requirements were predictable. The FDA did not complete many of the mandates of the MDA. For example, by 1987, the FDA had not completed the classification of pre-1976 devices (a task finished in 1988 [Hutt et al., 2007, *supra* note 11, 986]), had not promulgated any performance standards for any of the roughly 1,100 types of devices placed in Class II, and had not

⁷⁸FFDCA § 520(e), 21 USC § 360j(e) (2006).

⁷⁹FFDCA § 502(q)–(r), 21 USC § 352(q)–(r); § 704(a), 21 USC § 374(a) (2006).

⁸⁰Implementation of the Medical Device Amendments of 1976, 41 Fed. Reg. 22,620 (June 4, 1976).

⁸¹*Becton, Dickinson & Co. v. FDA*, 589 F.2d 1175, 1182 (2d Cir. 1978); *In re Establishment Inspection Portex, Inc.*, 595 F.2d 84, 86–87 (1st Cir. 1979).

⁸²45 Fed. Reg. 65,619 (Oct. 3, 1980).

⁸³46 Fed. Reg. 57,568 (Nov. 24, 1981).

⁸⁴FFDCA § 515(d)(1)(B)(ii), 21 USC § 360e(d)(1)(B)(ii) (2006).

⁸⁵FFDCA § 514(a)(2)(B)(v), 21 USC § 360d(a)(2)(B)(v) (2006).

called for PMAs for any of some 140 preamendment Class III devices.⁸⁶ As discussed below, even after amendment of the MDA in 1990 to ease the burdens on the FDA, the problems in completing implementation of the MDA remained a major concern to Congress. The Subcommittee on Health and the Environment of the House Committee on Energy and Commerce requested an audit by GAO regarding the FDA's rule-making process in 1990. In April 1992, the subcommittee held a hearing devoted to that subject, citing delays in issuing regulations called for by various FDA statutes passed in 1983, 1984, and 1990. The chairman opened the hearing by stating that "the most troubling area of concern is implementation of the 1976 medical device amendments."⁸⁷ As a result of the FDA's delays in issuing a particular regulation called for by the 1990 amendments to the MDA, Congress was compelled to pass a new law in June 1992 to revise the 1990 amendments to provide additional time for implementation.⁸⁸

The most important consequence of the combination of limited resources and burdensome administrative procedures was the evolution of the 510(k) clearance process from a transitional tool for preclearance of postamendment Class III devices and unclassified types of devices to a permanent and dominant means of premarket review of most devices. By broadening the concept of substantial equivalence, the FDA used the 510(k) system to avoid requiring PMAs for (or down-classifying) many new and novel devices that would have been placed in Class III. More than 80% of postamendment Class III devices had entered the market on the basis of a 510(k) showing substantial equivalence to a preamendment device.⁸⁹ Moreover, many postamendment devices were being found substantially equivalent to preamendment devices in Class I or Class II notwithstanding substantial technologic changes. For example, computerization of many devices occurred under the 510(k) system (IOM, 2010, pp. 22–28). The result was that some 10 years after enactment most Class II and Class III devices still underwent a premarket review that appeared to be no more rigorous than that applied to Class I devices.⁹⁰

⁸⁶Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 345 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

⁸⁷*Food and Drug Administration Oversight: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 102d Cong., pt. 2, at 1 (1992).

⁸⁸1992 MDA, Pub. L. No. 102-300, 106 Stat. 238. The regulation related to reporting by user facilities of device-related adverse medical events.

⁸⁹Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 344 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

⁹⁰Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug*

To understand why and how that situation came about, one must start with a literal reading of the MDA and a narrow interpretation of “substantial equivalence.” For a proposed postamendment device, the manufacturer was to submit sufficient information for the FDA to determine whether it was substantially equivalent to a preamendment device. If the FDA found that the new product was not substantially equivalent, it was automatically placed in Class III. The manufacturer would then have to submit a PMA or file a petition to reclassify the device into Class I or Class II.⁹¹ The PMA was totally new and untested but was perceived as likely to be burdensome for both industry and the FDA in cost and time to prepare and review. The alternative, device reclassification, was one of the processes for which Congress had demanded extensive notice-and-comment rule-making procedures and advisory-committee participation; in addition, a reclassification from Class III to Class II could be conditioned on the completion of additional lengthy procedures to establish a performance standard for the device.⁹²

Both alternatives proved very demanding of FDA resources. In 1987, the agency told Congress that it estimated that the staff time needed to review a PMA was more than 1,200 hours on average. In contrast, the FDA said that it needed only 20 hours, on the average, to review a 510(k) submission.⁹³ That is, for every two products required to undergo PMA review instead of 510(k) review, the FDA might need an additional full-time employee. At that time, the agency received more than 5,000 510(k) and 100 PMA submissions a year. If even 1% more of the new products were subject to PMA rather than the 510(k) clearance process, the FDA could need 25 additional employees. The agency also believed that issuance of performance standards for Class II devices would be even more burdensome, estimating that 40 staff-years (not staff-hours) would be required to develop a single performance standard (GAO, 1988b, p. 4).

Without more resources, the FDA chose to use the 510(k) clearance process as much as possible. To do that, the FDA implemented a liberal reading of substantial equivalence. In addition, it began to let manufacturers file 510(k)s that relied on a sequential chain of prior 510(k)s for postamendment devices to build the substantial equivalence to a preamendment device.

The FDA's preclearance strategy was clearly described by Congress's former OTA in a 1984 report:

Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce, 100th Cong. 337 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

⁹¹FFDCA § 513(f), 21 USC § 360c(f).

⁹²FFDCA § 513(e), 21 USC § 360c(e).

⁹³*Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce, 100th Cong., 384 (1987) (statement of James S. Benson, Deputy Director, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services).*

The 510k process, together with a determination of substantial equivalence, has been used extensively for postamendment devices to avoid Class III designation and its automatic requirement for premarket approval, or to avoid the involved rulemaking process necessary to reclassify such devices from Class III to Class I or II.

Use of the substantial equivalence clause to permit the marketing of devices without premarket approval has been encouraged by FDA's regulations and practices. First [for product modifications, FDA limited the requirement for a 510(k) submission to] "changes that could *significantly* affect the safety or effectiveness of the device" [emphasis added]. . . .

Second, FDA allows manufacturers to trace back through a chain of substantially equivalent postamendment devices to a device on the market before the amendments were enacted. . . . This practice has been labeled "piggybacking" or, alternatively, "equivalence creep". . . .

Third, the amount of data required to show substantial equivalence varies widely, depending on the device. (OTA, 1984, p. 104)

The data cited by OTA confirm the idea that the FDA seemed inclined to find substantial equivalence as often as possible (see Table A-1).

The percentage of 510(k) submissions found to be not substantially equivalent (NSE) has remained in the range of 2–4% throughout the life of the program. In the period FY 1988–1990, the percentage found NSE was about 2.0%.⁹⁴ From FY 1989 through FY 1996, it continued in the same low range (see Table A-2).

In the period FY 2004–2009, the submissions found NSE were 3–4%, and the submissions subject to other disposition rose from 9% to 17% (FDA, 2010, p. 39).

The category "Other Disposition or Open" includes 510(k) submissions on which a final judgment of equivalence had not been made, those on which additional information was requested and the applicant could not respond in 30 days, those withdrawn by the applicant, those not accepted for filing by CDRH, those forwarded to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research for review, those deleted (for example, duplicates), those exempted by regulation from 510(k) review, those involving products that are not actively regulated (for example, a general-purpose article, an unfinished product, or not a device), and other administrative dispositions. It is possible that the percentage of

⁹⁴SUBCOMM. ON OVERSIGHT AND INVESTIGATIONS OF THE H. COMM. ON ENERGY AND COMMERCE, 103D CONG., LESS THAN THE SUM OF ITS PARTS: REFORMS NEEDED IN THE ORGANIZATION, MANAGEMENT, AND RESOURCES OF THE FOOD AND DRUG ADMINISTRATION'S CENTER FOR DEVICES AND RADIOLOGICAL HEALTH 42 (Comm. Print 103-N).

TABLE A-1 510(k) Submissions and Those Found Not Substantially Equivalent, 1976–1982

Year	No. 510(k) Submissions	No. 510(k) Submissions Found Not Substantially Equivalent	Percentage of 510(k) Submissions Found Not Substantially Equivalent
1976 (7 months)	1,362	8	0.6%
1977	2,427	47	1.9%
1978	2,180	43	2.0%
1979	2,714	44	1.6%
1980	3,316	73	2.2%
1981	3,652	63	1.7%
1982	3,780	55	1.5%
Total	19,431	333	1.7%

SOURCE: Adapted from OTA, 1984, p. 104.

510(k) submissions that are found to be substantially equivalent is a better statistic by which to measure the success of the system in excluding inappropriate products from the market. This approach assumes, however, that all the “other dispositions” are the result of a likely finding of NSE, that is, that persons filing these 510(k) submissions withdraw them or fail to respond to questions because they recognize the futility of proceeding. This category undoubtedly includes 510(k) submissions that would ultimately have been judged NSE, but the available data do not permit further analysis.

The lack of volatility in the NSE rate over a 30-year period is remarkable, given that it covers different generations of reviewers and companies filing 510(k) submissions, emerging novel technologies, elimination of 510(k) reviews for most Class I devices, much higher average numbers of pages per submission, increasing demands for clinical and laboratory data, and evolving review practices and guidance. A congressional report in 1993 asserted, without citation, that CDRH had an “unofficial” policy that disapproval of 510(k) submissions should not exceed 2 percent.⁹⁵ If true, that would support the view that, for at least some period, the FDA consciously sought to minimize its PMA workload by relying on the 510(k) clearance process. In any event, the history casts doubt on the reliability of a long chain of prior 510(k) clearances for making decisions today. If a product should have been processed by a PMA in the 1980s or 1990s but went through the 510(k) clearance process instead, any substantially equivalent product in 2010 must by law be cleared by the 510(k) clearance process.

⁹⁵SUBCOMM. ON OVERSIGHT AND INVESTIGATIONS OF THE H. COMM. ON ENERGY AND COMMERCE, 103D CONG., LESS THAN THE SUM OF ITS PARTS: REFORMS NEEDED IN THE ORGANIZATION, MANAGEMENT, AND RESOURCES OF THE FOOD AND DRUG ADMINISTRATION’S CENTER FOR DEVICES AND RADIOLOGICAL HEALTH 39 (Comm. Print 103-N).

TABLE A-2 510(k) Submissions and Those Found Not Substantially Equivalent, FY 1989–1996

Year	No. 510(k) Submissions	No. 510(k) Submissions Found Not Substantially Equivalent		Percentage of 510(k) Submissions Found Not Substantially Equivalent		No. 510(k) Submissions of Other Disposition or Open		Percentage of 510(k) Submissions of Other Disposition or Open	
		Found Not Substantially Equivalent	Equivalent	Substantially Equivalent	Not Substantially Equivalent	Disposition or Open	Disposition or Open	Disposition or Open	Disposition or Open
1989	7,023	108		1.5%		1,657		23.6%	
1990	5,835	142		2.4%		1,062		18.2%	
1991	5,774	146		2.5%		1,115		19.3%	
1992	6,533	202		3.1%		1,419		21.7%	
1993	6,310	109		1.7%		1,449		23.0%	
1994	6,450	96		1.5%		1,527		23.7%	
1995	6,078	71		1.2%		1,218		20.0%	
1996	5,316	43		0.8%		1,200		22.6%	
Total	49,319	917		1.9%		10,647		21.6%	

SOURCE: Adapted from GAO, 1997b, p. 7.

Congressional Oversight of the Food and Drug Administration's Implementation of the Medical Device Amendments in 1982–1990

Congress monitored how the 1976 amendments were implemented by the FDA through various arms: GAO, OTA, the Subcommittee on Health and the Environment and the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, and the Senate Committee on Labor and Human Resources. Reports and hearings demonstrate that many of the issues facing medical-device regulation now were identified and examined more than 2 decades ago.

1982–1983 Subcommittee on Oversight and Investigations Hearings and May 1983 Report

The Subcommittee on Oversight and Investigations conducted a hearing on the implementation of the MDA on July 16, 1982, and launched its own investigation.⁹⁶ In the following year, the subcommittee issued a report titled *Medical Device Regulation: The FDA's Neglected Child*.⁹⁷ It was harshly critical of the agency, as can be seen in the chairman's letter of transmittal to the committee, which described the report as "a picture of bureaucratic neglect for public health and safety that shocks the conscience," opined that the FDA had shown "a cavalier disregard for the potential consequences" of its inaction, and cited many examples of "FDA's derelictions in the device area."⁹⁸

The subcommittee made a series of findings, including⁹⁹

1. Through negligence, or by intention, the FDA has failed to implement major provisions of the [MDA]:
 - a. The agency has lost control of the medical device classification process, failing to complete in 6 years major tasks for which Congress allocated 1 year.
 - b. The agency has not even begun to develop standards to assure safe, effective performance of class II devices.
 - c. The agency has not required manufacturers of "old" class III devices to submit premarket approval applications.
 - d. The agency has adopted no valid, reliable adverse experience report-

⁹⁶*FDA Oversight: Medical Devices, Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 97th Cong. (1982).

⁹⁷SUBCOMM. ON OVERSIGHT AND INVESTIGATIONS OF THE H. COMM. ON ENERGY AND COMMERCE, 98TH CONG., *MEDICAL DEVICE REGULATION: THE FDA'S NEGLECTED CHILD* (Comm. Print 98-F).

⁹⁸*Id.* at iii–iv (Letter of Transmittal, John D. Dingell, Chairman, H. Subcomm. on Oversight and Investigations).

⁹⁹*Id.* at 4.

- ing system to inform the agency of device-related deaths, injuries, or device defects.
- e. The agency has used its significant new authority to notify professionals and users of devices of risks of harm a mere three times in 6 years, and it has used its authority to order repair, replacement, or refund but once.
2. The FDA is relying almost exclusively on “General Controls” to regulate devices when it previously determined that such general controls were inadequate.
 3. As a consequence, the FDA is not equipped and, therefore, is unable to assure the American people that many medical devices currently on the market—and relied upon to treat disease and to sustain life—are safe and effective.
 4. By failing to “restrict” devices in order to address problems caused through their misuse by inappropriately trained persons or in poorly equipped facilities, the FDA has failed to deal with the most frequent source of device-related injuries.

The subcommittee interpreted the MDA to compel performance standards for all Class II devices without discretion on the part of the FDA. The subcommittee also rejected an argument made by the FDA that performance standards might not be essential for Class II devices because there were no problems with the devices. In the subcommittee’s view, the absence of an effective system for identifying device-related adverse experiences precluded the FDA from drawing any such conclusion.¹⁰⁰ It further rejected, as contrary to the risk-prevention approach adopted by Congress in the MDA,¹⁰¹ the idea of deferring performance standards until a public-health problem was identified.

The subcommittee made no specific legislative recommendations, but it did call attention to the “practical impossibility” of performance standards for each of the more than 1,000 types of Class II devices. It therefore suggested that “consideration be given to alternatives that recognize that although devices placed into Class II may pose significant risks to health, with respect to some devices those risks may be addressed by a species of controls less comprehensive than the mandatory performance standards now required by section 514.”¹⁰² One option identified was to divide Class II into two classes, for which one (Class II) would be required to have performance standards and the other (Class II-A) would not have to have

¹⁰⁰*Id.* at 15.

¹⁰¹*Id.* at 16.

¹⁰²*Id.* at 5.

performance standards but could be subject to greater regulatory controls than Class I devices (for example, classification as a restricted device or increased mandatory adverse-experience reporting).¹⁰³ The primary problem, in the subcommittee's view, was that the FDA had classified too many devices into Class II and some way had to be found to reduce the number subject to mandatory performance standards.¹⁰⁴

September 1983 General Accounting Office Report

GAO issued a report to Congress titled *Federal Regulation of Medical Devices—Problems Still to be Overcome* in fall 1983 on the basis of a survey of 68 people in a variety of disciplines in the private sector who were considered experts on medical devices, including consumer groups, health care, biomedical research, bioengineering, law, trade associations, and manufacturing (GAO, 1983). The survey was designed to explore the extent of MDA implementation, the effects on innovation and manufacturing costs, and the general focus and extent of federal regulation. GAO also examined the FDA's information systems and interviewed FDA officials.

GAO concluded that the FDA needed a comprehensive information system on the safety of medical devices in the marketplace; that development of performance standards for Class II devices—numbering more than 1,000 at that point—would be time-consuming and expensive, likely to become obsolete quickly, and perhaps unnecessary to ensure the safety and effectiveness of devices; that review of preamendment Class III devices would take many years; and that new risky devices in Class II and Class III were not being assessed for safety and effectiveness but only for substantial equivalence to preamendment devices. GAO observed, with regard to the 510(k) clearance process, that “FDA's position is that ‘substantial equivalency’ does not require a determination of safety and effectiveness” (GAO, 1983, p. 55) and that the “major problem cited by experts we interviewed was that the substantial equivalence review provides no assurance of device safety and effectiveness” (GAO, 1983, p. 56).

Among its recommendations, GAO proposed that the FDA “(1) identify new Class II devices that pose health risks significant enough to require examination of safety and effectiveness data as part of an adequate finding of substantial equivalency and (2) develop guidelines for determining and documenting the safety and effectiveness of such devices” (GAO, 1983, p. 63). The FDA and its parent agency, HHS, disagreed with that particular recommendation, stating the following (GAO, 1983, pp. 75–76):

This [proposed] procedure would significantly alter the classification and

¹⁰³*Id.* at 17.

¹⁰⁴*Id.* at 18.

marketing procedures established in the amendments for Class II devices in a way not intended by the Congress.

* * * *

As opposed to being a means for determining safety and effectiveness, the 510(k) process was intended by Congress to be simply a screening mechanism that would: (1) allow "substantially equivalent" post-Amendment devices to enter the market and be regulated like their pre-Amendment predecessors; and (2) identify "not substantially equivalent" post-Amendment devices and automatically place them in the premarket approval category. . . .

We also believe FDA is applying the "substantial equivalency" test in a manner consistent with Congressional intent, though Congress' instructions are not explicit on the interpretation of this term.

GAO's response to the FDA's comments was to reaffirm its recommendation and emphasize the deficiency in the current system (GAO, 1983, pp. v-vi, pp. 63-64):

GAO's rationale for recommending safety and effectiveness documentation for certain Class II devices is similar to the reasons why safety and effectiveness reviews are necessary for Class III devices. In neither case has FDA determined the safety and effectiveness of the preenactment devices for which the new device is considered substantially equivalent. For Class III devices, FDA is required to make a safety and effectiveness determination for the preenactment device, but has not done so. For new Class II devices, FDA must determine whether they are substantially equivalent to a preenactment device, but is not required to establish whether the preenactment device is safe and effective. Consequently, a safety and effectiveness review is not conducted for either the substantially equivalent or preenactment device. Implementation of GAO's recommendation would provide assurances that risky new Class II devices are safe and effective.

February 1984 House Subcommittee on Health and the Environment Hearing

On February 24, 1984, the Subcommittee on Health and Environment of the House Committee on Energy and Commerce held its first oversight hearing on implementation of the MDA.¹⁰⁵ GAO presented a summary of its 1983 report and was followed by the FDA, represented by the acting

¹⁰⁵*Medical Device Amendments of 1976: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce, 98th Cong. (1984) (cited in SUBCOMM. ON*

commissioner and the director of CDRH. The FDA's testimony highlighted these points:

- The FDA was “considering the development of instructions that describe what constitutes appropriate content for a 510(k) submission.”¹⁰⁶ In other words, in the first 8 years of the 510(k) program, there was neither a standardized format nor a set of required contents for these submissions.
- Issuance of performance standards for all Class II devices was neither possible nor essential. First, it was too resource-intensive. “This assessment is based on the experience we have gained in the radiation area, where we have found, for example, that it takes roughly 40 person-years to develop a performance standard, and about 23 person-years annually to enforce it. [And] we have found that technological advances force us to revise many standards periodically, thus further depleting our resources.”¹⁰⁷ “More important, it is unnecessary to develop federally mandated performance standards for all of these devices in order to protect the public health.”¹⁰⁸
- Down-classification of Class II device types to Class I, to avoid performance standards, would not reduce the resource burden. “In order to reclassify, the law requires that we assemble scientific evidence of safety and effectiveness, with a notice-and-comment rulemaking procedure in the Federal Register for each device.”¹⁰⁹
- Subdividing Class II into Class II and Class II-A, as suggested by the Subcommittee on Oversight and Investigations report of May 1983, “would still be too inflexible, simply substituting one set of requirements for another. Most important, the FDA does not need additional class II-A authority, since we already have sufficient authority under the general controls of class I to carry out any of the actions stipulated in the class II-A proposal [that is, imposing restrictions under the restricted-device provisions, increasing medical-device adverse-event reporting, and subjecting firms to periodic checking by FDA].”¹¹⁰
- The FDA did request new legislation to eliminate what it perceived as a statutory obligation to promulgate performance standards for every

HEALTH AND THE ENV'T OF THE H. COMM. ON ENERGY AND COMMERCE, 98TH CONG., HEALTH AND THE ENVIRONMENT MISCELLANEOUS—PART 2 (Comm. Print 98-108)).

¹⁰⁶*Id.* at 296 (statement of Mark Novitch, M.D., Acting Commissioner of Food and Drugs, Food and Drug Administration, Department of Health and Human Services).

¹⁰⁷*Id.* at 296–297.

¹⁰⁸*Id.* at 297.

¹⁰⁹*Id.*

¹¹⁰*Id.*

Class II device type. “Class II devices [are] those for which mandatory performance standards are presently required by the law.”¹¹¹ “We believe that changes in the law are needed which would give [FDA] discretionary authority to select those devices requiring mandatory standards. . . . With the addition of discretionary authority, the Agency will be able to deal realistically with the class II device problem without compromising public health.”¹¹²

- For Class II devices for which performance standards were needed, the process for establishing the standards should be streamlined.¹¹³
- Although final regulations for manufacturer reporting of device-related adverse medical experiences—medical-device reporting (MDR)—had not yet been promulgated, even when in place they would not provide a complete picture. “In fact, many device problems in the field can be attributed to how the device is used, as opposed to how it is manufactured. Thus, we need a monitoring system which is complementary to MDR, but which relies on information from hospitals, practitioners, and consumers. This voluntary system, [which] we call the Device Experience Network, or DEN, is already in place, and is yielding approximately 2,500 reports per year, each of which is assessed, and many of which require action.”¹¹⁴

In his questioning, the chairman of the subcommittee noted that one of the major device-industry trade associations, the Health Industry Manufacturers Association (HIMA), was going to testify later in the hearing to the effect that the FDA was not required by the MDA to promulgate performance standards for all Class II devices. The FDA chief counsel set forth the FDA’s view of the law:

A device is placed in class II because a determination has been made that the class I general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device.

That determination having been made and the device having been put into class II, you have got an outstanding determination that the controls provided under class I are insufficient, and a determination that a performance standard should be set for the device. We think that that combination of requirements appearing in the two classes . . . do not give us discretion to decline ever to promulgate a standard for a device that is in class II.

The argument that we do have such discretion is based on the initial

¹¹¹*Id.* at 305.

¹¹²*Id.* at 297.

¹¹³*Id.*

¹¹⁴*Id.* at 298.

language of section 514, which says [FDA] may, by regulation, issue a performance standard. We don't regard the word "may" there as giving us the discretion not to establish a performance standard.

We can rank order devices, and establish a priority list . . . but we think the act, as currently drafted, does contemplate that unless we are given the discretion to stop at some point, we have to keep going down that list and establish performance standards.¹¹⁵

The testimony of HIMA on this point presents a different view:

As to the nature of FDA's standards-writing authority, we agree that there is ambiguity as to whether FDA must write standards for Class II products or whether it may write such standards. . . . The legislative history contains little to clarify explicitly this apparent contradiction, so we are left with attempting to reconcile these two statutory provisions.¹¹⁶

HIMA goes on to construct an argument that concludes that although the definition of Class II stated that a performance standard is necessary to provide reasonable assurance of safety and effectiveness, it does not require that this standard be promulgated by the FDA.¹¹⁷

March and September 1984 House Subcommittee on Oversight and Investigations Hearings

The Subcommittee on Oversight and Investigations held two hearings focused on device-related adverse-medical-experience reporting and the long delay in the FDA's issuance of regulations to implement the authority conferred in the MDA in 1976.¹¹⁸ The FDA promulgated its MDR regulations, to take effect in 3 months (on December 14, 1984), just days before the second hearing, which was held on September 26, 1984.¹¹⁹ The subcommittee took credit for getting that action completed. The presiding representative, Albert Gore, said:

This subcommittee . . . is painfully aware of the history of this particular

¹¹⁵*Id.* at 330 (answer of Thomas Scarlett, chief counsel, Food and Drug Administration, Department of Health and Human Services).

¹¹⁶*Id.* at 350 (testimony of the Health Industry Manufacturers Association).

¹¹⁷*Id.*

¹¹⁸*Failed Pacemaker Leads: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 98th Cong. (1984) (Comm. Print 98-134); *Anesthesia Machine Failures: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 98th Cong. (1984) (Comm. Print 98-188).

¹¹⁹Medical Device Reporting, 49 Fed. Reg. 36,326 (Sept. 14, 1984) (to be codified at 21 CFR pt. 600, 803, 1002-03).

regulation. It was first proposed in November 1980, some 4 years after the passage of the law referred to earlier. Shortly after this administration took office, that regulation which had been proposed was pulled back and was sent to disappear into what I have referred to as the black hole of cost-benefit analysis, and the regulation remained in that black hole until the subcommittee's 1982 hearings and the 1983 report.

On May 27, 1983, the agency repropoed the mandatory device reporting regulation. True to his word, then Acting Commissioner Novitch submitted the regulation to Secretary [of Health and Human Services Margaret] Heckler in March of this year, and there the regulation sat until on August 24 the subcommittee contacted Secretary Heckler again and said we are going to have another hearing; 3 days later, she signed the regulation, and it was at last published in the Federal Register.¹²⁰

October 1984 Office of Technology Assessment Report

At the request of the Senate Committee on Labor and Human Resources in 1982, OTA, a congressional office that existed from 1972 to 1995 to provide objective and authoritative analysis of complex scientific and technical issues, convened an expert advisory panel to examine federal policies involving the medical-device industry. Its final report covered characteristics of the device industry, policies affecting payment for devices and health care, research on and development of devices, the use of medical devices, and regulation by the FDA (OTA, 1984). OTA made a number of salient observations about the 510(k) clearance process:

- The FDA had used the 510(k) clearance process and its interpretation of substantial equivalence to avoid putting many products into Class III and the concomitant workload that PMA would necessitate (OTA, 1984, p. 104).
- OTA was particularly concerned about the devices in Class II. More than 60% of the device types so far classified had been placed in Class II, and that suggested that it was a catch-all category, offering the appearance of more controls than the minimum requirements imposed on Class I while not subjecting products to the full demands that PMA required of a Class III device. The criteria for Class II were that general controls could not be expected to provide reasonable assurance of safety and effectiveness of a device and that there was sufficient evidence to establish a performance standard to provide

¹²⁰*Anesthesia Machine Failures: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce, 98th Cong. 39 (1984) (Comm. Print 98-188).*

such assurance. But the FDA had not established a single performance standard and was unlikely to be able to promulgate many, because of the procedural requirements in the law. OTA opined that the “fact that no mandatory performance standards have been issued casts doubts on [the] conclusion” that the device types placed in Class II met the statutory criteria. “Regardless of whether or not the 1976 statute requires, rather than permits, the use of performance standards, the fact remains that, as a practical matter, there is little possibility that standards can be formulated for the large number of device types that have been placed in Class II. If performance standards were meant to be selectively used, the designation of so many device types as Class II and the resulting perception of the futility of such an exercise have been damaging to the FDA’s efforts, no matter what the rationale” (OTA, 1984, p. 120). Moreover, in the absence of performance standards, all Class II devices had been, in effect, regulated as though they were Class I devices (OTA, 1984, pp. 109–110).

- Between 1977 and 1982, a total of 128 Class III products had gained PMA approval, and another 1,007 Class III products had entered the market via the 510(k) clearance process on findings of substantial equivalence to preamendment Class III devices that had yet to undergo PMA review for safety and effectiveness (OTA, 1984, pp. 112–114). Thus, almost 90% of the Class III products entering the market in this period were also in effect regulated as though they were Class I devices.
- The FDA did not deem a 510(k) clearance either an approval for marketing or a finding of safety or efficacy. “FDA’s Office of General Counsel does not consider a finding of ‘substantial equivalence’ an approval. A device is considered approved once a determination is made that it is safe and effective. The 510(k) method of obtaining the FDA’s permission to market a device is basically a determination that the device is substantially equivalent to a preamendments device, and the FDA has no choice but to allow it to be marketed; it is not a determination that the device is safe and effective” (OTA, 1984, p. 128).

OTA laid out options for policy-makers to consider but did not recommend any specific actions. One option would “recognize the two-tiered regulatory approach that has been applied to medical devices rather than the three-tiered approach originally built into the law” (OTA, 1984, p. 127). Other options to reduce or eliminate the challenges of performance standards for all Class II devices were to give the FDA authority to use methods other than performance standards to regulate Class II devices, to create a new category in Class II that would be regulated through methods other

than performance standards, and to encourage the FDA to reclassify most Class II devices into either Class I or Class III.

OTA had an interesting perspective on the use of substantial equivalence. It believed that the practice would gradually fade away, stating:

as new generations of postamendments devices diverge more and more from their preamendments antecedents, it will be harder for manufacturers to use the substantial equivalence method of market entry. It will also be harder to practice "piggybacking," in which a postamendments device is compared to another postamendments device and, through a chain of other postamendments devices, eventually compared to a preamendments device.

More immediately, FDA's Office of Chief Counsel has stated that such "piggybacking" is not authorized by the amendments, and if the practice of piggybacking ceases, more postamendments devices will eventually be placed in Class III, and their manufacturers will have to go through the full premarket approval process or petition FDA for reclassification. (OTA, 1984, p. 130)

Thus, OTA assumed that existing procedures for determining substantial equivalence would be self-limiting. OTA offered two other options for consideration: eliminate the automatic classification of novel devices into Class III (allowing the FDA instead to make the initial classification at the time of initial notification) and develop procedures for reviewing modifications of commercially available devices distinct from procedures for reviewing new devices (assuming, apparently, that changes made in marketed products by existing suppliers raised fewer and narrower issues than the introduction of novel devices and new manufacturers) (OTA, 1984, pp. 130–131).

December 1986 General Accounting Office Report

The December 1986 GAO report was the first in a long series, stretching over more than 20 years, that has been critical of the FDA's MDR system. GAO undertook a study of the FDA's systems for monitoring device safety before the December 1984 implementation of mandatory manufacturing reporting of adverse experiences associated with medical devices. It found that hospitals report only about half the experiences to anyone (the FDA, manufacturers, or third-party organizations). Furthermore, information given to representatives of manufacturers rarely got to the companies' central files, from where they might be sent to the FDA. It concluded that the FDA learns about less than 1% of hospital-based device-related injuries. GAO recommended that the FDA establish a voluntary postmarketing surveillance system involving a representative sample of hospitals (GAO, 1986).

May 1987 House Subcommittee on Health and the Environment Hearing

On May 4, 1987, the Subcommittee on Health and the Environment held a hearing on the FDA's implementation of the MDA.¹²¹ GAO testified before the FDA, focusing on the 1986 report, but adding that it did not believe that the FDA's recent MDR regulations would solve the deficiencies identified in the report inasmuch as the agency was relying on reporting by manufacturers; too many opportunities existed for the communication of adverse-experience information to break down before it got to the manufacturer.¹²²

The chairman of the subcommittee, in a memorandum to its members, identified a number of concerns, including the absence of performance standards for Class II devices, the failure of the FDA to require PMAs for preamendment Class III devices and reliance on the 510(k) clearance process instead, the paucity of postamendment devices approved by PMA, the apparent increase in device recalls, and MDR reports.¹²³ He singled out the expansion of the concept of substantial equivalence in the 510(k) program, about which he stated:

As interpreted by FDA, section 510(k) permits post-1976 devices that have the same intended use as a pre-1976 device to enter the market so long as they are as safe and effective [as] the pre-1976 device.

Under FDA's approach, devices that come onto the market fifty years after passage of the law will only have to demonstrate that they are as safe and effective as devices on the market before 1976. Even today, more than ten years after the law was passed, major technological improvements have occurred with many medical devices. Yet, under FDA's 510(k) approach, new devices need not incorporate these improvements; they need only be as safe and effective as similar devices on the market before 1976.¹²⁴

The FDA was represented by James Benson, deputy director of CDRH, who did not have prepared testimony but explained the actions recently taken by CDRH to address the issues of concern to the subcommittee. He testified that "it takes us [CDRH] 1200 staff hours to review a PMA,

¹²¹*Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 331 (1987).

¹²²*Id.* at 365-83 (statement of Eleanor Chelimsky, General Accounting Office).

¹²³Memorandum Re: Medical Device Hearing, May 4, 1987, *Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 336-47 (1987) (referred to in the statement of Rep. Henry A. Waxman, Chairman, H. Subcomm. on Health and the Env't).

¹²⁴*Id.* at 339.

but about 20 hours to review a 510(k). . . .”¹²⁵ That statement has been cited ever since to distinguish the rigor of the PMA process from that of the 510(k) mechanism. The FDA has advised the present committee that it believes that those numbers are no longer accurate (Desjardins, 2011). Mr. Benson went on to say:

We basically . . . have taken a very hard look at the 510(k) clearance process. *Only recently* have we been able to get some guidance into the hands of the reviewers and . . . manufacturers. . . . That guidance basically says that a new product must be *at least* as safe as and as efficacious as prior products on the market [emphasis added].¹²⁶

The chairman of the subcommittee asked Mr. Benson to confirm (which he did) that the FDA policy was that the “bottomline test is still the safety and effectiveness of the original [pre-1976] device.”¹²⁷

July 1988 General Accounting Office Report

The chairman of the House Subcommittee on Health and the Environment asked GAO to evaluate the FDA’s estimates of the number of device-related adverse-experience reports that would follow if reporting by user facilities (for example, hospitals, ambulatory surgical centers, and nursing homes) were mandated and to evaluate the CDRH resource needs to process such reports. GAO reported that user reporting would increase the volume of reports but not permanently and that the FDA could achieve greater internal efficiencies in processing the reports (GAO, 1988a). (As will be seen below, 8 months later and again in 1997, GAO would reach different conclusions about the FDA’s resource requirements to operate the MDR system.)

August 1988 General Accounting Office Report

In response to another request of the chairman of the House Subcommittee on Health and the Environment, GAO undertook a study from 1986 to 1987 and issued a report in August 1988 titled *Medical Devices: FDA’s 510(k) Operations Could Be Improved* (GAO, 1988b). The report reflected GAO’s first in-depth examination of the 510(k) process as it operated. GAO found that the policies governing premarket notification were

¹²⁵*Medical Devices and Drug Issues: Hearing Before the Subcomm. on Health and the Env’t of the H. Comm. on Energy and Commerce*, 100th Cong. 384 (1987) (statement of James S. Benson, Deputy Director, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services).

¹²⁶*Id.* at 385.

¹²⁷*Id.*

generally adequate but that reviewing divisions differed concerning when to request additional information from 510(k) submitters. That observation suggested to GAO a lack of clear officewide policy and coordination among the divisions (GAO, 1988b, p. 3). It also identified deficiencies in internal documentation of 510(k) decisions (GAO, 1988b, p. 3). GAO recommended steps to improve consistency in decision-making and documentation practices (GAO, 1988b, p. 5).

GAO identified several problems with the 510(k) clearance process and its substantial-equivalence standard. First, GAO discussed the ambiguity of the term *substantial equivalence*:

The statute does not define or otherwise elaborate on the meaning of the term substantial equivalence. The relevant legislative history can be read in different ways. Under one reading, whenever a device about to be marketed varies from a pre-1976 device in its materials, design or energy sources, the product would be found not substantially equivalent and would be subject to premarket approval. Under a less restrictive reading, only variations that could, or do, materially affect safety or effectiveness should result in a “not substantially equivalent” decision. In any case, a determination of substantial equivalence in the premarket notification process does not mean that a device is safe and effective; it merely indicates that the device under review is not less safe and effective than a comparable pre-1976 device. (GAO, 1988b, pp. 2–3)

Second, it advised that relying on preamendment devices for determining substantial equivalence was problematic in that it excluded consideration of later superior devices. “If manufacturers can demonstrate that their devices are used for the same purposes and perform as well as products marketed prior to 1976, the FDA must [under current law] find the products to be substantially equivalent even if there are other products already on the market that ‘work better’” (GAO, 1988b, p. 4). GAO recommended that Congress amend the 1976 MDA to require the FDA to determine substantial equivalence on the basis of a comparison with a currently marketed device instead of a preamendment device (GAO, 1988b, p. 5). The auditors also suggested that Congress consider “clarifying the extent to which FDA should evaluate, within the premarket notification process, the effects of changes in medical devices on their safety and effectiveness” (GAO, 1988b, p. 5).

GAO underscored the absence of any performance standards for Class II devices and the high percentage of Class III devices for which PMA reviews of safety and effectiveness had not yet begun. The FDA advised GAO that the agency estimated that it took 1,200 staff-hours to review each PMA and 40 staff-years to develop a single performance standard (GAO, 1988b, p. 4). GAO observed that “additional resources will be required” for the

FDA to make more rapid progress in implementing these aspects of the 1976 amendments (GAO, 1988b, p. 4). Moreover, GAO observed that

because of these implementation problems, devices in class II and class III may be marketed through premarket notification without having to meet the additional requirements appropriate to their classification. As a result, FDA must place more reliance on premarket notification to control access of medical devices to the market than would otherwise be the case. (GAO, 1988b, p. 4)

To address that issue, GAO suggested that Congress might consider “developing alternative approaches to the regulation of devices currently placed in classes II and III” (GAO, 1988b, p. 5).

February 1989 General Accounting Office Report

Before the 1987 hearing, the chairman of the Subcommittee on Health and the Environment sought a GAO review of the FDA’s implementation of the MDR regulation. The report in response concluded that the MDR regulation had increased the number of device-related adverse-experience reports but that CDRH’s internal system could not handle the higher volume, so the potential effectiveness of the MDR regulation had not been fully realized. Moreover, GAO found that many manufacturers (perhaps one-third of those registered) were not aware of the MDR reporting requirements (which were effective in December 1984) and reporting across the industry was inconsistent, sometimes excessive, and often insufficient to comply with the rules. (GAO, 1989d, p. 2)

August and October 1989 General Accounting Office Reports

The chairman of the Subcommittee on Health and the Environment asked GAO to analyze medical-device recalls to identify the types of devices that had been recalled, the problems for which they were recalled, and the mode of market entry for the problem devices. GAO issued an interim report in August 1989 describing the data that had been gathered and a report in October providing further analyses (GAO, 1989b, 1989c). GAO found that design problems were the most common reason for Class I recalls;¹²⁸ that many recalls were undertaken by manufacturers without notice to the FDA, so roughly half the Class I recalls were brought to the FDA’s attention from sources other than the manufacturers (for example, competitors, users, and FDA inspections); and that the device problems that led to the recalls often

¹²⁸FDA classifies recalls in reverse order of devices. Class I recalls denote the greatest immediate risk to the health, whereas Class I devices present the lowest inherent risk to health.

were not reported to the FDA as MDRs, notwithstanding the requirement under the MDR regulations for such reporting.

November 1989 House Subcommittee on Health and the Environment Hearing

The Subcommittee on Health and the Environment held a hearing on legislation to address problems with the 1976 MDA and its implementation by the FDA.¹²⁹

The first witnesses were from GAO, including the comptroller general, who heads that agency. He criticized the premarket testing and clearance of devices, citing four basic problems with the system as it was operating¹³⁰:

One is that many of the pre-1976 devices were never tested themselves. Two, you have use of an old and often outdated comparison base. Three, you have a lack of definition of what is substantial equivalence. Four, [you have] FDA's failure to develop standards for medium risk devices or to implement premarket requirements for high risk devices.

GAO also criticized the system of postmarketing surveillance on the basis of its recent reports to Congress.¹³¹

The acting FDA commissioner then testified. He commented on a proposed bill then pending before the subcommittee; the bill was a successor to a bill that passed the House in 1988 but died in the Senate. The acting commissioner commended the bill on many points, including codifying the FDA's policies regarding substantial equivalence in the 510(k) clearance process and eliminating a requirement for the promulgation of performance standards for Class II devices. "The bill would give FDA discretion to apply one or more 'special controls' to a given device problem."¹³² The agency, however, opposed the legislative proposal for user reporting of adverse device-related events as unnecessary and infeasible, stating that the system for manufacturer reporting was preferred by the FDA.¹³³

¹²⁹*Medical Device Safety: Hearings Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 101st Cong. (1989–1990).

¹³⁰*Id.* at 33 (statements of Charles A. Bowsher, comptroller general, and Eleanor Chelinsky, assistant comptroller general, General Accounting Office).

¹³¹*Id.*

¹³²*Id.* at 173 (statement of James S. Benson, Acting Commissioner, Food and Drug Administration).

¹³³*Id.* at 177.

February 1990 Subcommittee on Oversight and Investigations Hearing

The Subcommittee on Oversight and Investigations issued a report and held a hearing in February 1990 in which the FDA was severely criticized for failing to use the investigative and enforcement powers it already had and for failing to seek additional statutory authority that it needed in the regulation of the Bjork-Shiley heart valve.¹³⁴ This hearing set the final political stage for the first revisions to the MDA.

July 1990 Department of Health and Human Services Inspector General Report,

The HHS inspector general reviewed the FDA's internal controls over the 510(k) program at the request of the assistant secretary for health after the scandals that emerged in the late 1980s related to the FDA's approval process for generic drugs. The inspector general audited the 510(k) clearance process to identify potential weaknesses that could lead to similar problems.

The inspector general began by noting the purpose of the 510(k) system:

The primary objective of the premarket notification 510(k) clearance process is to determine whether a new or modified device is "substantially equivalent" to a device already on the market. A determination of substantial equivalence does not mean that a device is safe and effective; rather, it is an indication that the device is not less safe nor less effective than a comparable device.¹³⁵

The final report covers a variety of concerns, two of which are related to the reliability of the decision-making process (and the validity of devices cleared earlier as proper predicates). The inspector general determined that the FDA

- does not use certain critical information to make determinations of substantial equivalence, such as review of the product sample, verification of testing data, and premarket inspections of manufacturer facilities; [and]

¹³⁴STAFF OF SUBCOMM. ON OVERSIGHT AND INVESTIGATIONS OF THE H. COMM. ON ENERGY AND COMMERCE, 101ST CONG., *THE BJORK-SHILEY HEART VALVE: "EARN AS YOU LEARN"—SHILEY INC.'S BREACH OF THE HONOR SYSTEM AND FDA'S FAILURE IN MEDICAL DEVICE REGULATION* (Comm. Print 101-R); *FDA and the Medical Device Industry: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 101st Cong. (1990).

¹³⁵Memorandum Re: Internal Control Weaknesses in the Food and Drug Administration's Medical Device 510(k) Review Process, from the HHS inspector general to the HHS assistant secretary for health (July 5, 1990) 1, fn. 1

- lacks a comprehensive quality control program to independently evaluate and critique the adequacy of reviewed submissions. . . .¹³⁶

THE SAFE MEDICAL DEVICES ACT OF 1990

The House had originally passed new device legislation in 1988, but the Senate took no action. In October 1990, both the House and Senate passed bills to revise the MDA; these were reconciled in conference, and a final bill, the Safe Medical Devices Act of 1990 (SMDA 1990), passed Congress and was signed into law on November 28.¹³⁷

The initial House report on the bill explained the goal of the legislation as follows:

Since the comprehensive medical device law was enacted in 1976, difficulties have persisted in the implementation of the law. These implementation problems appear to be the result of: (1) complexities in the law; (2) the manner in which FDA interpreted certain provisions of the 1976 law; and (3) limited resources. The purpose of this legislation is to modify the underlying law in ways that will result in greater protection of the public health.¹³⁸

The 1990 legislation included provisions that restructured the premarket-review scheme and separately expanded the scope of the “general controls” applicable to devices without regard to their classification.

Changes in Premarket Review Processes

The SMDA took a variety of steps to modify the original 1976 MDA structure for assessing the safety and effectiveness of devices before marketing. The three most relevant to the present discussion involve the regulatory standards and related requirements that differentiate Class I and Class II devices, the definition of substantial equivalence, and the retrospective review of the safety and effectiveness of preamendment Class III devices.

Definition of Class II; Replacement of Mandatory Performance Standards Requirements for All Class II Devices with Discretionary Special Controls Authority

Congress recognized both that the FDA had been unable to promulgate performance standards and that performance standards were not necessar-

¹³⁶*Id.* at 2.

¹³⁷SMDA, Pub. L. No. 101-629, 104 Stat. 4511.

¹³⁸H.R. REP. NO. 101-808, at 13 (1990); *see also* S. REP. NO. 101-513, at 14-15 (1990).

ily the best or only regulatory tool to ensure the safety and effectiveness of devices for which general controls were not sufficient. Moreover, other tools might permit devices to be placed in Class II when, without the availability of such tools, Class III status would be necessary. Accordingly, it revised the definition of Class II to read as follows:

A device which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as [FDA] deems necessary to provide such assurance. For a device that is purported or represented to be for a use in supporting or sustaining human life, [FDA] shall examine and identify the special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance.¹³⁹

The apparent inconsistency between the definition of Class II devices (those for which general controls were insufficient and for which additional controls would be necessary) and the discretionary power of the FDA to promulgate performance standards or use its other powers (epitomized by the use of the word *may*) was resolved by a legislative compromise. Class II would include devices on which information was sufficient to establish one or more special controls¹⁴⁰—but the FDA did not have to adopt any of those controls unless it concluded that it was necessary to provide reasonable assurance of safety and effectiveness.¹⁴¹ That solution alleviated resource burdens on the agency but left open the question of whether the safety and effectiveness of a Class II device could not be ensured if only general controls applied, as the statutory definition seemed to suggest.¹⁴²

Congress also provided that the FDA could itself initiate a reclassification proceeding and not have to wait for a petition from a manufacturer.¹⁴³ In addition, the 1990 law simplified the process for issuing performance standards applicable to Class II devices by adopting the usual notice-and-comment rule-making process.¹⁴⁴ The FDA could establish other special

¹³⁹FFDCA § 513(i)(1), 21 USC § 360c(i)(1) (2006) (as modified by SMDA, § 5(a)(2), 104 Stat. at 4517-18).

¹⁴⁰FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

¹⁴¹FFDCA § 514(a)(1), 21 USC § 360d(a)(1) (2006).

¹⁴²FFDCA § 513(a)(1)(B), 21 USC § 360c(a)(1)(B) (2006).

¹⁴³FFDCA § 513(f)(2)(A), 21 USC § 360c(f)(2)(A) (2006) (as modified by SMDA § 5(b), 104 Stat. at 4518).

¹⁴⁴FFDCA § 514(b), 21 USC 360d(b) (2006) (as modified by SMDA § 6(a), 104 Stat. at

controls through different mechanisms and procedures, some of which are less burdensome than those required for performance standards.

Finally, the revised definition authorizes the FDA to require clinical data as part of 510(k) submissions, resolving another ambiguity in the original 1976 law (Cooper, 1987, p. 192).

Definition of Substantial Equivalence

Congress had not defined *substantial equivalence* in the 1976 law. By adopting a broad reading of the phrase, set forth in a guidance document in 1986,¹⁴⁵ the FDA used the 510(k) system to avoid requiring PMAs for (or alternatively down-classifying) many new and novel devices that would have been placed in Class III.

For instance, the agency allowed a new device to be determined to be substantially equivalent to a preamendment device, notwithstanding important technological differences, if the new device was as safe and effective as the antecedent. To make that comparison, the FDA could require appropriate comparative data, including clinical studies, from the 510(k) submitter. The guidance is worth quoting at length because it was endorsed by Congress in the 1990 legislative history.

As a matter of practice, CDRH generally considers a device to be SE [substantially equivalent] to a predicate device if, in comparison to the predicate device:

- the new device has the same intended use. . . ; and,
- the new device has the same technological characteristics, (i.e., same materials, design, energy source, etc.); or, it has new technological characteristics that could not affect safety or effectiveness; or
- it has new technological characteristics that could affect safety or effectiveness, and

—there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and

— there are data to demonstrate that the new technological features have not diminished safety or effectiveness.¹⁴⁶

* * * *

4519).

¹⁴⁵Guidance on the CDRH Premarket Notification Review Program (K86-3) (June 30, 1986) available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm>.

¹⁴⁶*Id.* at 2.

[F]rom a scientific perspective, to determine which technological changes are consequential, the Center considers whether:

- the new device poses the same type of questions¹⁴⁷ about safety or effectiveness as a predicate device;
- there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and
- there are data to demonstrate that new technological characteristics have not diminished safety or effectiveness.¹⁴⁸

The requirements of Section 510(k) of the act are intended not only to notify the FDA that a device is about to be marketed but also primarily to enable the FDA to determine whether the device is substantially equivalent to one already in commercial distribution. To fulfill that responsibility, CDRH requires that a 510(k) submission include descriptive data needed to understand a new device's intended use, physical composition, method of operation, specifications, performance claims, and other factors. Similar information about the device with which the new device is being compared may also be required. In addition, under some circumstances, the center requires performance-testing information (that is, data from bench, animal, or clinical tests), to determine whether a device performs according to its description.

Although CDRH has concluded that it should sometimes require performance-testing data to confirm that a new device is substantially equivalent, the 510(k) review process is not a substitute for premarket approval, and the center does not attempt to address all the issues that would be answered in a PMA application in its review of 510(k) submissions. Data in a 510(k) submission should show comparability of a new device with a predicate device,¹⁴⁹ whereas demonstration, in an absolute sense, of a device's safety and effectiveness is reserved for PMAs.

The FDA also permitted a postamendment device to claim substantial equivalence to a preamendment device through an implied string of precedents from other postamendment devices previously cleared by 510(k) review, a process known as piggybacking. The guidance stated

¹⁴⁷The guidance gave examples to illustrate that "same type of questions" meant issues raised by both the predicate and the new device and would be answered in the same manner (for example, whether electronic components of electrocardiographs accurately represent the electrical activity of the heart, regardless of whether displayed in an analog visual manner or in digital format).

¹⁴⁸*Id.* at 3.

¹⁴⁹*Id.* at 4.

The Center does not routinely require that manufacturers perform research to determine what specific predicate devices were available in 1976, or were available at the time a post-Amendments device was reclassified from class III to class I or II; nor does the Center routinely require that all 510(k)s initially provide information on a predicate device. Instead, the Center requires submitters to provide information that compares the new device to a marketed device of a similar type, regardless of whether this marketed device was marketed before or after enactment of the Amendments, or before or after a type of post-Amendments device was reclassified.¹⁵⁰

Whether the FDA could lawfully assess comparative safety and effectiveness to determine substantial equivalence, could require clinical studies to demonstrate comparable safety and effectiveness, or could permit piggy-backing under the 510(k) law as written in 1976 were controversial issues (Cooper, 1987; OTA, 1984).

By 1989, the agency was sufficiently concerned that an adverse court ruling on its interpretation of substantial equivalence would cripple the 510(k) clearance process, and thus force many new devices into the PMA system, that it sought legislative ratification of its policy.¹⁵¹ In 1990, Congress obliged, adding the following language to the statute:

A. For purposes of determinations of substantial equivalence . . . the term “substantially equivalent” or “substantial equivalence” means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that [FDA] by order has found that the device –

- (i) has the same technological characteristics as the predicate device, or
- (ii) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including clinical data if deemed necessary by [FDA], that demonstrates that the device is as safe and effective as a legally marketed device and (II) does not raise different questions of safety and efficacy than the predicate device.

B.–For purposes of subparagraph (A), the term “different technological characteristics” means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.¹⁵²

¹⁵⁰*Id.* at 2.

¹⁵¹*Medical Device Safety: Hearings Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 101st Cong. 172 (1989–1990) (statement of James S. Benson, Acting Commissioner, Food and Drug Administration).

¹⁵²FFDCA § 513(i)(1), 21 USC § 360c(i)(1) (2006) (added by SMDA § 12, 104 Stat. at 4523).

The reports of the House and Senate committees responsible for this legislation make clear that the intent was to codify the FDA's practice.¹⁵³ Congress understood that the statutory change would permit the agency to consider the safety and effectiveness of a device when determining substantial equivalence¹⁵⁴ and added another provision that required a 510(k) sponsor to submit either a summary of "any information respecting safety and effectiveness" (which the FDA would make public within 30 days of finding substantial equivalence) or a statement that such information would be available to any person on request.¹⁵⁵ Arguably, those changes represented an effort by Congress and the FDA to redesign the 510(k) system to include an evaluation of safety and effectiveness of all new devices.¹⁵⁶ Nevertheless, the statutory scope of such an evaluation was very limited. The standard for substantial equivalence permitted the agency to use safety and effectiveness data only when a new device offered technologic characteristics that differed from those of the predicate device. Moreover, Congress made clear that it did not believe that a substantial-equivalence determination was a finding of safety or effectiveness. The House report states

A determination by the FDA that a device is substantially equivalent to another device is a final agency action under the substantial equivalent provisions, but it does not preclude further agency action regarding safety and effectiveness.¹⁵⁷

The new language provided a solid legal basis for the FDA's 510(k) policies. The agency could incorporate some degree of safety and effectiveness assessments into the 510(k) system because it would now be required to find "by order" that a new device with different technological characteristics was at least as safe and effective as its predicate. To do so, it clearly could require appropriate safety and effectiveness information, including clinical studies when necessary. And piggybacking was automatic because a new product could rely on any lawfully marketed device as a predicate.

Congress had now formally opened the door for safer or more effective medical devices to reach the market via the 510(k) pathway. By being permitted to show that its product was "as safe and effective as" a predicate (instead of merely having substantially equivalent safety and effectiveness), the 510(k) submitter could improve the safety and effectiveness of a type of device without triggering the risk of being found NSE and having to undergo

¹⁵³H.R. REP. NO. 101-808, at 25; S. REP. NO. 101-513 at 41.

¹⁵⁴*Id.*

¹⁵⁵FDCA § 513(i)(3), 21 USC § 360c(i)(3) (2006) (added by SMDA § 12, 104 Stat. at 4523).

¹⁵⁶As will be discussed below in the section "The Supreme Court Considers the 510(k) Clearance Process," the FDA and the solicitor general did not make this argument to the Supreme Court in 1996.

¹⁵⁷H.R. REP. NO. 101-808, at 25.

a PMA review. A new device might be both *superior* to its predicate and *substantially equivalent* to it. The legislative history noted, “In this way, the standard for safety and effectiveness in a determination of substantial equivalence will evolve slowly as the prevailing level on the market changes, rather than being tied solely to comparison with a pre-1976 device.”¹⁵⁸

Congress did not define *predicate device* but prohibited the use as a predicate of any device removed from the market by the FDA or found by a court to have been adulterated or misbranded.¹⁵⁹ Thus, the 1990 amendments did not require reliance on the best available predicate device, so a new product that was truly inferior to the current state of the art might still enter the market—if the manufacturer could identify any predicate that had not been removed from the market and to which it was substantially equivalent.¹⁶⁰ In this regard, the law did not force innovation. Indeed, by that amendment, Congress also made every prior 510(k) decision a precedent binding on the FDA, which had no explicit power to rescind these actions. Only if the FDA banned a marketed device or had a court adjudicate the device as adulterated or misbranded could the device no longer serve as a predicate.

Requirement for Final Food and Drug Administration Action on a 510(k) Submission

Under the MDA, a company had to give the FDA 90 days’ notice before introducing a new product to the market through the submission of a 510(k) notification. If the FDA failed to respond to the filing in the 90-day window, the manufacturer was free to launch the product beginning on the 91st day. Congress eliminated the risk that a product could enter medical use by the FDA’s failure to act by requiring the 510(k) submitter to wait for a written response (called an order) from the FDA stating that its product was substantially equivalent before commercializing it.¹⁶¹

Preamendment Class III Devices

Both the House and the Senate committees considering the 1990 legislation were displeased by the FDA’s lack of progress since 1976 in pro-

¹⁵⁸H.R. REP. NO. 101-808, at 25.

¹⁵⁹FFDCA § 513(i)(2), 21 USC § 360c(i)(2) (2006) (added by SMDA § 12, 104 Stat. at 4523).

¹⁶⁰In its 1988 bill, the House would have used the standard “as safe and effective as comparable devices which are currently sold in interstate commerce.” H.R. REP. NO. 100-782 at 4 and 23. Arguably, this standard would have been more rigorous than the one finally adopted.

¹⁶¹FFDCA § 513(i)(1)(A), 21 USC § 360c(i)(1)(A) (2006) (added by SMDA § 12, 104 Stat. at 4523).

mulgating regulations to require PMAs for, and then reviewing the safety and effectiveness of, preamendment Class III devices and devices that had entered the market as substantially equivalent to them.¹⁶² In conjunction with revising the definition of Class II, Congress authorized the FDA to reconsider all the preamendment devices that had originally been placed in Class III to reduce the number of device types that needed PMA review.¹⁶³ The agency was also directed “as promptly as possible” but no later than December 1, 1996, to establish a schedule for promulgation of regulations calling for PMAs of devices not down-classified to Class II that still used the 510(k) pathway to marketing.¹⁶⁴

The FDA was not, however, given a deadline by which to complete the PMA process for Class III preamendment devices not reclassified to Class II.

Changes in General (Postmarketing) Controls

Much of the momentum for legislation in 1988–1990 came from reports that the FDA had difficulties in learning about serious problems with marketed devices.¹⁶⁵ Thus, many of the provisions in the SMDA of 1990 focused on identifying issues of safety or lack of effectiveness sooner and giving the FDA additional tools to use when problems were encountered. As with the original 1976 law, these controls were applicable under the 1990 amendments without regard to the classification of a device for premarket review purposes.

User Reporting of Device Risks

A GAO study in 1986 revealed that hospitals often did not report potentially hazardous medical devices to the FDA or the manufacturers.¹⁶⁶ Even though manufacturers were required to investigate and report to the FDA information received from hospitals, physicians, patients, and others, the system would fail if users did not report to the manufacturers. To address that gap, Congress required “device user facilities”—defined as hospitals, ambulatory surgical facilities, nursing homes, and outpatient treatment facilities (but not physician offices)—to report to the FDA and to the manufacturer when a medical device caused or contributed to the death or serious

¹⁶²H.R. REP. NO. 101-808, at 14, 25-26; S. REP. NO. 101-513, at 14-15, 18.

¹⁶³FFDCA § 515(i), 21 USC § 360e(i) (2006) (added by SMDA § 4(b), 104 Stat. at 4515-17).

¹⁶⁴FFDCA § 515(i)(2), 21 USC § 360e(i)(2) (2006).

¹⁶⁵H.R. REP. NO. 101-808, at 14; S. REP. NO. 101-513, at 15-16.

¹⁶⁶H.R. REP. NO. 101-808, at 14 (citing (GAO, 1986)).

illness of a patient.¹⁶⁷ The FDA was directed to promulgate implementing regulations within 12 months.¹⁶⁸

Postmarket Surveillance

The FDA was given authority to require the manufacturer of any device initially introduced to commerce after 1990 to develop and conduct a surveillance plan if the device was a permanent implant whose failure might cause death or serious adverse health consequences, was intended to support or sustain human life, potentially presented a serious risk to human health, or was determined by the FDA to need surveillance to provide safety or effectiveness data or to protect public health.¹⁶⁹ The statute used the phrase *postmarket surveillance* to refer specifically and narrowly to these plans and did not include other safety monitoring and vigilance systems in the phrase. It did not specify any particular methods, but only that the protocol “will result in collection of useful data . . . to provide information necessary to protect the public health and to provide safety and effectiveness information for the device.”¹⁷⁰

Device Tracking

For any device whose failure would be reasonably likely to have serious health consequences and that was permanently implantable or was a life-sustaining or life-supporting device used outside a “device user facility,” the manufacturer was required to adopt a method of device tracking (such as a patient registry).¹⁷¹ The purpose of tracking was to maintain a system whereby an individual patient or end user (as well as the relevant physicians) could be notified of new risks and the devices could be recalled if necessary.¹⁷²

Reports of Removals and Corrections

The 1990 amendments required a device manufacturer to report to the FDA whenever it removed or corrected a device if that was done to reduce a risk to health posed by the device or to remedy a violation of the FFDCA caused by the device that might result in a risk to health.¹⁷³ (Corrections

¹⁶⁷FFDCA § 519(b), 21 USC § 360i(b) (2006) (added by SMDA § 2, 104 Stat. at 4511-13).

¹⁶⁸SMDA § 2(b), 104 Stat. at 4512-13.

¹⁶⁹FFDCA § 522, 21 USC § 360l (2006) (added by SMDA § 10, 104 Stat. at 4521-22).

¹⁷⁰FFDCA § 522(b), 21 USC § 360l(b) (2006) (added by SMDA § 10, 104 Stat. at 4522).

¹⁷¹FFDCA § 519(e), 21 USC § 360i(e) (2006) (added by SMDA § 3(b), 104 Stat. at 4514).

¹⁷²H.R. REP. NO. 101-808, at 23.

¹⁷³FFDCA § 519(f), 21 USC § 360i(f) (2006) (added by SMDA § 7, 107 Stat. at 4520).

might include, for example, software patches, replacement of parts, or revision of operating instructions or directions for use.) Congress intended the agency to become aware of actions taken by a manufacturer that suggested a potential public-health problem so that the agency could evaluate the device-related problem and the adequacy of the manufacturer's corrective actions.¹⁷⁴

Recall Authority

The FDA had previously relied on voluntary actions by manufacturers to recall devices believed to violate the law. In the event that a manufacturer failed to act, the agency could go to court to seek orders to seize the devices wherever they were found,¹⁷⁵ a costly and time-consuming effort in comparison with voluntary recalls. (The 1976 act empowered the FDA only to issue an administrative order detaining devices for up to 20 days to permit the judicial process for a seizure action to be completed.¹⁷⁶) The SMDA changed that situation substantially. The FDA could now order manufacturers (and others, including distributors and retailers) immediately to cease distribution of a device, to notify healthcare providers and device-user facilities to cease using the device, and to recall the device if there was a reasonable probability that the device would cause serious adverse health consequences or death.¹⁷⁷

Civil Money Penalties

The FFDCA of 1938, as amended by the MDA of 1976, created a limited array of sanctions to penalize individuals and companies that violated the law: criminal fines and imprisonment and seizure and forfeiture of violative products.¹⁷⁸ Those penalties could be imposed only after a trial in federal court, criminal punishments required proof beyond a reasonable doubt, and the threat of imprisonment did not apply to corporations. To enhance the FDA's enforcement credibility, Congress in 1990 provided that the FDA could also impose substantial civil money penalties by an administrative hearing without going to federal court for any violation of the law related to medical devices. The amounts authorized ranged up to \$15,000 for each violation and up to \$1 million for all violations adjudicated in a single proceeding.¹⁷⁹

¹⁷⁴S. REP. NO. 101-513, at 23; H.R. REP. NO. 101-808, at 29.

¹⁷⁵FFDCA § 304(a)(2)(D), (b), 21 USC § 334(a)(2)(D), (b) (2006).

¹⁷⁶FFDCA § 304(g), 21 USC § 334(g) (2006).

¹⁷⁷FFDCA § 518(e), 21 USC § 360h(e) (2006) (added by SMDA § 8, 104 Stat. at 4520-21).

¹⁷⁸FFDCA § 303(a), 21 USC § 333(a); § 304(a)-(d), 21 USC § 334(a)-(d) (2006).

¹⁷⁹FFDCA § 303(f), 21 USC § 333(f) (2006) (added by SMDA § 17, 104 Stat. at 4526-28).

Design Controls as Part of Good Manufacturing Practices

The 1976 MDA had authorized the FDA to issue regulations requiring that the methods used in and the facilities and controls used for the manufacture, storage, and installation of medical devices conformed to current good manufacturing practices (GMP) to ensure that the devices would be safe and effective and otherwise comply with FDA law.¹⁸⁰ The agency wanted to include as a GMP requirement the concept of design validation to require a manufacturer, as a preproduction control, to implement a process to demonstrate that the components of the device (singly or in combination) will perform in a manner consistent with their intended purpose. The FDA estimated that 44% of device recalls in 1983–1988 were related to product design problems. Design validation was already a recognized element of quality control in the European Community. But the FDA and Congress were concerned that the MDA might not provide sufficient authority.¹⁸¹ Accordingly, the 1990 amendments explicitly authorized language that the FDA's GMP regulations to require that "pre-production design validation (including a process to assess the performance of a device but not including an evaluation of the safety or effectiveness of a device)" also conform to "current good manufacturing practice."¹⁸²

DEVELOPMENTS IN 1990–1997

The Medical Device Amendments of 1992

The 1990 legislation directed the FDA to promulgate final regulations implementing the authority to require adverse–medical-event reporting by user facilities by May 28, 1992; if not, any proposed regulations would automatically become effective.¹⁸³ The FDA did not issue proposed regulations until March 27, 1992, so that left only 2 months for public comment and for implementation. Congress elected to extend the effective dates by 6 months (for the regulations) and 9 months (for implementation).¹⁸⁴

The failure to meet the statutory deadlines for issuance of regulations prompted both a GAO review and a congressional hearing before the House Subcommittee on Health and the Environment. GAO reported that in July 1990, the acting commissioner of the FDA had identified the following six

¹⁸⁰FFDCA § 520(f)(1)(A), 21 USC § 360j(f)(1)(A) (2006).

¹⁸¹H.R. REP. NO. 101-808, at 33.

¹⁸²FFDCA § 520(f)(1)(A), 21 USC § 360j(f)(1)(A) (2006) (as amended by SMDA § 18(e), 104 Stat. at 4529).

¹⁸³SMDA § 3(c), 104 Stat. at 4514-15.

¹⁸⁴1992 MDA § 2, 106 Stat. at 238.

factors that contributed to the delay in the rule-making process: (GAO, 1992, p. 7)

- Emergence of significant problems during the regulations development process that require reevaluation of previous agreements [within the FDA and with HHS and OMB] on regulation content.
- Competition among priorities within the agency, including with other regulatory and enforcement activities.
- Required reviews within the FDA, and by [HHS] and OMB.
- Need to coordinate with other agencies.
- Uncertainty as to the appropriate scope of review.
- Lack of resources.
- At the hearing, the FDA witnesses had testified about steps being undertaken to make the process more efficient.¹⁸⁵

The need to extend the deadline provided an opportunity for a number of linguistic and technical corrections and clarifications to be made in other parts of the SMDA of 1990.¹⁸⁶ None of them had a material effect on the provisions under discussion.

February 1993 Department of Health and Human Services Inspector General Report

In response to a request from the House Subcommittee on Oversight and Investigations, the HHS inspector general performed a follow-up review regarding the July 1990 report.¹⁸⁷ One topic addressed was the Office of the Inspector General's prior recommendation that the FDA establish "a quality control review system that involves independent review of completed 510(k) decisions by an FDA group . . . to evaluate and critique the adequacy of reviewed submissions."¹⁸⁸ The inspector general concluded that the steps taken by CDRH since 1990 "primarily focus on the 510(k) administrative process and not the scientific validity of the decisions made by the 510(k) reviewers. Also, quality control reviews of the 510(k) staff were not always documented."¹⁸⁹

The significance of that observation lies in the implicit findings, in both 1990 and 1993, that CDRH lacked a robust quality-assurance program to

¹⁸⁵*Food and Drug Administration Oversight: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 102d Cong., pt. 2 (1992).

¹⁸⁶1992 MDA §§ 3-4, 106 Stat. at 238-39.

¹⁸⁷Memorandum from the principal deputy inspector general to the acting assistant secretary for health, Re: Follow-Up Review on Internal Control Weaknesses in the Food and Drug Administration's Medical Device 510(k) Review Process (Feb. 26, 1993).

¹⁸⁸*Id.* at ii.

¹⁸⁹*Id.* at 19.

ensure both consistency and correctness in 510(k) decisions for at least the first 16 years after the MDA's enactment.

1992–1997 Changes in the Food and Drug Administration Environment Affecting Device Regulation

At least four events had an important effect on device regulation during the 1990s. First, in 1992, FDA Commissioner David Kessler asked a task force drawn largely from the Center for Drug Evaluation and Research (CDER), headed by Robert Temple, to conduct a review of the quality of clinical science submitted to CDRH in support of 510(k) submissions and PMA applications. The resulting report was critical, observing (albeit on the basis of a small sample of PMA applications and 510(k) submissions containing clinical data) that studies submitted in support often failed to meet fundamental scientific standards. For example, the studies did not describe their purposes or the hypotheses to be tested, they failed to consider the value of randomized control groups, and they contained numerous deficiencies in conduct, reporting, and analysis (FDA, 1993). The report recommended a definite but gradual upgrading in the quality of clinical studies to support PMA applications and 510(k) submissions. CDRH undertook to implement the recommendations soon afterward.

In parallel with those changes and the 1990 amendments that explicitly referenced clinical data as an element of 510(k) submissions, the percentage of 510(k) submissions for which the FDA requested clinical data soon rose from 5% to 15% (Merrill, 1994, p. 64).

Commissioner Kessler also pushed the “medicalization” of CDRH. From its inception before the passage of the MDA of 1976, the center's leadership had expertise in engineering and administration but not in medicine. In 1993, the commissioner appointed the first physician to head CDRH: D. Bruce Burlington, who had previously served in both CDER and the Center for Biologics Evaluation and Review (CBER). Also for the first time, a physician was appointed to head the Office of Device Evaluation. Medical personnel became more common among the device review staff and operations. When Burlington left CDRH in 1999, he was succeeded as permanent director by David Feigal, another physician with experience in both CBER and CDER. Every later permanent CDRH director has been a physician, and medically trained persons have led other key CDRH offices.

The third change in the environment occurred in November 1994, when the Republican Party won control of both houses of Congress. All the medical-device legislation to date had been drafted and enacted when the Democratic Party, which generally had been more inclined to favor government regulation, had been in the majority. Now the FDA legislation, budgets, and activities were to be overseen by a party that was traditionally

more skeptical of government regulation and more sympathetic to industry concerns about the claimed direction of device regulation.

Finally, after Congress codified the FDA's standard for substantial equivalence in the 1990 amendments, the agency broadened the standard even further. As was explained to the IOM committee

According to the statute, in the face of different technologic characteristics, the agency asks whether the differences raise new safety or effectiveness questions. If the answer is yes, the device is found to be not substantially equivalent. The agency has not applied the statutory language exactly but asks whether the new technology raises new *types* of questions about safety and effectiveness. The reason that that word *types* was added to the program guidance is that any change in technology can raise a new question. By asking about new types of questions, the agency has greater discretion in making some of its regulatory decisions. . . . Similarly, when considering whether a product is as safe and as effective as another product, the agency asks whether the risks that are inherent in the new technology can be mitigated. In other words, if the technology and the effect of the change on the actual use of the product are well understood, the agency does not automatically reclassify the device to make it subject to PMA; instead, it looks to mitigate risks. (IOM, 2010, p. 11)

Those interpretations continued the policy of minimizing the number of 510(k) submissions that were rejected.

The Supreme Court Considers the 510(k) Clearance Process

In 1996, the Supreme Court examined the 510(k) clearance process in some depth.¹⁹⁰ At issue was whether a civil private lawsuit by a patient against a manufacturer for injuries allegedly resulting from a device was barred by the pre-emption provisions of the 1976 MDA. The law said that a state could not establish a requirement with respect to a device related to safety or effectiveness of the device that was different from or in addition to those requirements imposed by the FDA law.¹⁹¹ In the product liability suit, the manufacturer argued that imposition of liability by a state court based in tort law had the effect of creating such requirements with respect to design of the device. The device in question was a postamendment Class III product cleared through the 510(k) clearance process. The Court therefore had to assess the legal effect of the 510(k) review to determine whether it did create such requirements.

Although the FDA was not a party to the suit, the US solicitor general

¹⁹⁰Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996).

¹⁹¹FFDCA § 521(a), 21 USC § 360k(a) (2006).

filed a brief against pre-emption that explained the federal government's official view of the 510(k) clearance process¹⁹²:

The clearance of a post-Amendments device under Section 510(k)—based on a determination that the device is substantially equivalent to a pre-Amendments Class III device—does not reflect a determination by the FDA that the device is safe and effective, much less a specific determination that the device's design is required to ensure its safety and effectiveness. “[A] determination of substantial equivalence . . . is not equivalent to an approval by the FDA of the device's safety and effectiveness.” H.R. Rep. No. 808 [101st Cong., 2d Sess. (1990)], at 14 . . . As the court of appeals observed, the FDA ordinarily will not have determined whether the pre-Amendments device was safe and effective (since the FDA lacked the general authority to do so prior to enactment of the Amendments). . . . Accordingly, FDA regulations specify that a substantial equivalence determination “does not in any way denote official approval of the device,” and that any representation conveying “an impression of official approval . . . is misleading and constitutes misbranding.”

In its opinion, the Court contrasted the “rigorous PMA review” with the 510(k) clearance process and found them “by no means comparable.” Going beyond the argument of the solicitor general, the Court observed that,¹⁹³

in contrast to the 1,200 hours necessary to complete a PMA review, the § 510(k) review is completed in an average of only 20 hours. . . . As one commentator noted: “The attraction of substantial equivalence to manufacturers is clear. [Section] 510(k) notification requires little information, rarely elicits a negative response from the FDA, and gets processed very quickly.”

Turning to the specific argument of the manufacturer, the majority opinion of the Court stated¹⁹⁴:

As the court below noted, “[t]he 510(k) process is focused on *equivalence*, not safety.” . . . As a result, “substantial equivalence determinations provide little protection to the public. These determinations simply compare a post-1976 device to a pre-1976 device to ascertain whether the later device is no more dangerous and no less effective than the earlier device. If the earlier device poses a severe risk or is ineffective, then the later device may also be risky or ineffective.” . . .

¹⁹²Brief for the United States as Amicus Curiae Supporting Respondents/Cross-Petitioners 19-20, *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) (No. 95-754) (some internal citations omitted).

¹⁹³*Lohr*, 518 U.S. at 478-79 (citations omitted).

¹⁹⁴*Id.* at 493-494 (internal citations omitted).

There is no suggestion in either the statutory scheme or the legislative history that the § 510(k) exemption process was intended to do anything other than maintain the status quo with respect to the marketing of existing medical devices and their substantial equivalents.

An opinion, representing the views of all the other justices, concurred that the 510(k) “process merely evaluates whether the Class III device at issue is substantially equivalent” to a preamendment device.¹⁹⁵

In sum, the Supreme Court found that the 510(k) clearance process did not provide a rigorous review for safety and effectiveness of a device but only determined the new device’s comparability with a predicate device, which itself may never have been assessed for safety or effectiveness. Thus, it established no design requirements that would conflict with and therefore pre-empt state law.

The Supreme Court revisited the pre-emptive effects of the MDA. In 2001, the Court considered whether a fraud on the agency could be a basis for liability under state law or instead was pre-empted because it would interfere with federal prerogatives to protect the agency’s own processes. A threshold issue in the case was whether a 510(k) submission that contained untrue statements could be material fraud on the FDA. The Court held that it did, but it did not appear to change its view of the limited role of the 510(k) as a premarket clearance process¹⁹⁶:

Admittedly, the § 510(k) process lacks the PMA review’s rigor: The former requires only a showing of substantial equivalence to a predicate device, while the latter involves a time-consuming inquiry into the risks and efficacy of each device. Nevertheless, to achieve its limited purpose, the § 510(k) process imposes upon applicants a variety of requirements that are designed to enable the FDA to make its statutorily required judgment as to whether the device qualifies under this exception.

In 2008, the Court revisited the issue of pre-emption of liability claims by injured patients based on theories of design defects, failure to test, and lack of adequate warnings. In this case, however, the device was a Class III device that had undergone full PMA review and approval. The Court relied on its 1996 analysis comparing the “limited review” in the 510(k) clearance process with the “rigorous” PMA review; the latter imposed numerous and specific requirements on the design, testing, labeling, and other aspects of the manufacture, modification, and distribution of the approved device. Under those circumstances, the Court held that because state tort law could impose requirements related to the safety and effectiveness of the device different

¹⁹⁵*Id.* at 513.

¹⁹⁶*Buckman Co. v. Plaintiffs’ Legal Committee*, 531 U.S. 341, 348–349 (2001).

from or in addition to those imposed by the PMA process under the MDA, the state law would be pre-empted.¹⁹⁷

January 1997 General Accounting Office Report

GAO undertook an extended examination of the FDA's adverse-medical-event reporting system in light of the changes directed by the SMDA of 1990 (GAO, 1997a). It concluded:

Although the amount of information reported to FDA about medical device problems has increased dramatically since SMDA 90 was enacted, FDA does not systematically act to ensure that the reported problems receive prompt attention and appropriate resolution. As a result, FDA's adverse event reporting system is not providing an early warning about problem medical devices as SMDA 90 intended. (GAO, 1997a, p. 2)

GAO observed a long-term increase in the number of reports received by the FDA: the "increased volume made it difficult for FDA to process and review reports in a timely manner" (GAO, 1997a, p. 3). In addition, the FDA was not routinely documenting any corrective actions it (or manufacturers) took to address reported problems (GAO, 1997a, p. 3). Although GAO did not make any recommendations, it did recite a number of steps that the FDA was already taking to improve its system.

THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997

A variety of bills addressing congressional concerns about FDA regulation of foods, drugs, and medical devices were consolidated and passed as the FDA Modernization Act of 1997.¹⁹⁸ The device-related provisions modified both premarket and postmarket controls generally in the direction of restricting the FDA's preclearance authorities to accelerate the pace of technology transfer.

Modifications Regarding Premarket Review of Devices

Congress concluded that the FDA regulatory system was not keeping pace with medical innovation. "In a number of cases, for both 510(k)-cleared and PMA products, increased requirements that are burdensome, expensive, and time-consuming have delayed patients' access to promis-

¹⁹⁷Riegel v. Medtronic, Inc., 552 U.S. 312, 330 (2008).

¹⁹⁸Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) [hereinafter FDAMA]).

ing new devices.”¹⁹⁹ Furthermore, the total number of days for reviewing both 510(k) and PMA applications remained well above what Congress demanded in existing law. For example, the FDA averaged 110 days in FY 1996 to review a 510(k), down from a high of 184 days in FY 1994 but still higher than the 90 days called for in the statute.²⁰⁰ For PMAs, the average review time in FY 1996 was 572 days, down from a high of 649 in FY 1994 but also higher than the statutory 180-day limit.²⁰¹ Many of the changes made in 1997 were designed to reduce the FDA's workload and permit concentration of resources on devices that presented greater potential for harm. Some also reflected a concern that the changes in CDRH resulting from the Temple report and the infusion of medical personnel into senior CDRH management had led to an undue emphasis on clinical-trial data to support PMA applications and 510(k) submissions. The overall thrust of the 1997 amendments was to limit the FDA's discretion and authority in regulating the device industry.

Elimination of 510(k) Requirements for Most Class I and Some Class II Devices

Congress exempted from 510(k) notification requirements all Class I devices except for those “intended for a use which is of substantial importance in preventing impairment of human health” or “present[ing] a potential unreasonable risk of illness or injury.”²⁰²

The new law also directed the FDA (within 60 days of enactment) to identify each type of device in Class II for which a 510(k) submission would not be necessary to provide reasonable assurance of safety and effectiveness. Those identified would be exempt from 510(k) requirements as soon as the FDA announced its decision to exempt them.²⁰³ In addition, the FDA was authorized to exempt additional types of Class II devices from 510(k) submission in the future on the initiative of the agency or on petition by an interested person.²⁰⁴

¹⁹⁹H.R. REP. NO. 105-307, at 13 (1997).

²⁰⁰The number of review days is not the same as the number of days invested in reviewing a submission. The former is a calculation of the number of days between receipt of a submission and when it is finally acted on, omitting the number of days that FDA is waiting for responses to questions from the person making the submission. The latter looks only at the time that FDA employees are engaged in the review of the submission.

²⁰¹*Id.* at 14.

²⁰²FFDCA § 510(l), 21 USC § 360(l) (2006) (added by FDAMA, § 206(a), 111 Stat. 2338-39 (1997)).

²⁰³FFDCA § 510(m)(1), 21 USC § 360(m)(1) (2006) (added by FDAMA § 206(a), 111 Stat. at 2338-39).

²⁰⁴FFDCA § 510(m)(2), 21 USC § 369(m)(2) (2006) (added by FDAMA § 206(a), 111 Stat. at 2338-39).

The results of that change could be described as creating a class of devices (mostly in Class I and some in Class II) for which no preclearance is required, confirming a large subset of Class II for devices that would not be subject to any special control (that is, requiring only a 510(k) review showing substantial equivalence to a predicate device, as was the case for Class I devices under the 1976 MDA), and establishing another subset of Class II devices more akin to the original 1976 vision of Class II that combined 510(k) preclearance with one or more of the special controls envisioned by the 1976 and 1990 amendments. Thus, Class II had become divided, for practical purposes, into three groups: “Class IIA” (no preclearance and no special controls required; that is, effectively Class I), “Class IIB” (preclearance required but without special controls), and “Class IIC” (both preclearance and controls required). Given that the FDA had issued few special controls on Class II devices, the decision to exempt some Class II devices even from 510(k) notification requirements raises the question whether these devices should ever have been in Class II.

Authorization of Third-Party Review of 510(k) Submissions for Other Class I and Class II Devices

Congress directed the FDA to establish a scheme whereby third parties could be accredited to perform 510(k) reviews for any Class I or Class II device for which a 510(k) submission was still required other than Class II devices intended to be permanently implantable or life-sustaining or life-supporting or for which clinical data are required.²⁰⁵

Evaluation of Automatic Class III Designations

The new law required the FDA to evaluate whether a new device that, after submission of a 510(k) notification by the sponsor, was determined to be NSE to another device and therefore was automatically placed in Class III could be classified into Class I or Class II immediately without having to undergo PMA review.²⁰⁶ That process, now called the *de novo* 510(k), would be triggered by a request from the 510(k) submitter and have to be completed within 60 days. In the *de novo* process, the issue presented to the FDA is simply whether the device meets the criteria for Class I or Class II, in which case it is classified as a new device and becomes a predicate to which later devices may refer.

²⁰⁵FFDCA § 523, 21 USC § 360m (2006) (added by FDAMA § 210, 111 Stat. at 2342-45).

²⁰⁶FFDCA § 513(f)(2), 21 USC § 360c(f)(2) (2006) (added by FDAMA § 207, 111 Stat. at 2340).

Limitation of Food and Drug Administration Authority to Withhold 510(k) Clearance Because of Failure to Comply with Other FFDCA Requirements

Congress understood that the FDA had undertaken a policy of withholding clearance of a 510(k) submission when an inspection of the manufacturer revealed GMP violations. To countermand that use of FDA authority, the 1997 law required the agency to act on the 510(k) submission without regard to the manufacturer's failure to comply with any other provision of the FFDCA "unrelated to a substantial equivalence decision." To be clear, Congress went on to say that "including a finding that the facility in which the device is manufactured is not in compliance with good manufacturing requirements . . . (other than a finding that there is a substantial likelihood that the failure to comply . . . will potentially present a serious risk to human health)."²⁰⁷

Restriction of Scope of Review to Proposed Indications for Use

In response to complaints that the agency was denying 510(k) clearances because of potential "off-label" uses, Congress specified that the FDA was to make determinations solely on the indications for use proposed by the manufacturer in the labeling with the 510(k) submission.²⁰⁸ The new law did, however, permit the agency to require warnings in labeling with respect to off-label uses if there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling and that use could cause harm. That special authority could be exercised only by the director of the Office of Device Evaluation, not by any subordinate managers.

Restriction of Scope of Review to Least Burdensome Means of Demonstrating Equivalence

The SMDA of 1990 had codified the FDA's approach to determining substantial equivalence, including authorizing the FDA to request additional information in the 510(k) submission to confirm equivalence.²⁰⁹ The FDA had already, on its own initiative, revised the substantial-equivalence standard to limit requests for data only when the differences presented new

²⁰⁷FFDCA § 513(f)(5), 21 USC § 360c(f)(5) (2006) (added by FDAMA § 206(b), 111 Stat. at 2339).

²⁰⁸FFDCA § 513(i)(1)(E), 21 USC § 360e(i)(1)(E) (2006) (added by FDAMA § 205(b), 111 Stat. at 2337-38).

²⁰⁹FFDCA § 513(i)(1)(A)(ii), 21 USC § 360c(i)(1)(A)(ii) (2006) ("the information submitted that the device is substantially equivalent to such other device, including clinical data if required by [FDA], demonstrates that the device is as safe and effective as such other device which is currently being sold").

types of questions or new risks that could not be mitigated (IOM, 2010, p. 11). In 1997, Congress restricted the agency further, specifying that the FDA could request information only if it were necessary to make the substantial-equivalence determination. Moreover, in making such a request, the FDA has to “consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.”²¹⁰

Device Classification (and Reduction in Scope of PMA Review Regarding Effectiveness) to Consider Substitution of Postmarket Controls

The 1997 law directed the FDA to “consider the extent to which reliance on postmarket controls may expedite the classification of devices” into Class I or Class II instead of Class III.²¹¹

Congress ordered that “in making a determination of a reasonable assurance of effectiveness” in reviewing a PMA, the FDA must “consider whether the extent of data that otherwise would be required for approval . . . with respect to effectiveness can be reduced through reliance on post-market controls.”²¹²

The legislation also provided for collaborative determinations by the FDA and a PMA applicant of the type of scientific evidence needed to approve a particular PMA. The law created a process for meetings, internal appeals of scientific disagreements between a company and the FDA reviewers, and binding written FDA commitments on the evidence needed.²¹³ Congress was again interested in reducing unnecessary clinical testing of medical devices. It provided²¹⁴:

Any clinical data, including one or more well-controlled investigations, specified in writing by [FDA] for demonstrating a reasonable assurance of device effectiveness shall be specified as [a] result of a determination by [FDA] that such data are necessary to establish device effectiveness. [FDA] shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.

²¹⁰FFDCA § 513(i)(1)(D), 21 USC § 360c(i)(1)(D) (2006) (added by FDAMA § 205(b), 111 Stat. at 2337).

²¹¹FFDCA § 513(i)(C), 21 USC § 360c(i)(C) (2006) (added by FDAMA § 205(b), 111 Stat. at 2337).

²¹²FFDCA § 513(a)(3)(C), 21 USC § 360c(a)(3)(C) (2006) (added by FDAMA § 205(a), 111 Stat. at 2336).

²¹³FFDCA § 513(a)(3)(D), 21 USC § 360c(a)(3)(D) (2006) (added by FDAMA § 205(a), 111 Stat. at 2336-37); FFDCA § 562, 21 USC § 360bbb-1 (2006) (added by FDAMA § 404, 111 Stat. at 2368).

²¹⁴FFDCA § 513(a)(3)(D)(ii), 21 USC § 360c(a)(3)(D)(ii) (2006) (added by FDAMA § 205(a), 111 Stat. at 2337).

Finally, the new law clarified that establishing effectiveness would require only one clinical investigation.²¹⁵ The legislative history of these provisions contains the following explanation, which underscores the negative congressional reaction to the Temple report of 1993, which had recommended greater consideration of randomized controlled studies to support medical-device safety and effectiveness²¹⁶:

The Committee believes that [these amendments] are necessary to and consistent with improving communication between the FDA and regulated persons, increasing regulatory efficiency, and decreasing the length of product review and approval. In particular, the Committee is aware of examples where the FDA has requested inappropriate types of clinical testing for certain breakthrough devices and is concerned about instances in which the agency has required sponsors to conduct unnecessary randomized clinical studies to demonstrate device effectiveness. Although randomized clinical testing may be the best means of demonstrating device effectiveness for some products, the Committee is informed that such testing is often unnecessary to demonstrate effectiveness for many devices.

Alternative Procedures for Setting Performance Standards for Class II Devices

The 1997 law provided that the FDA could recognize an appropriate performance standard established by a nationally or internationally recognized organization engaged in standard development. In lieu of an extended notice-and-comment rule-making, the FDA could simply issue a notice of recognition.²¹⁷ In addition, Congress provided a simplified process for applicants to certify compliance with the standard.²¹⁸

Priority PMA Review for Important New Devices

Congress directed the FDA to provide review priority for medical devices that represented breakthrough technologies, for which no approved alternatives existed, that offered substantial advantages over existing ap-

²¹⁵FFDCA § 513(a)(3)(A), 21 USC § 360c(a)(3)(A) (2006) (revised by FDAMA § 217, 111 Stat. at 2350).

²¹⁶H.R. REP. NO. 105-307, at 24 (1997).

²¹⁷FFDCA § 514(c)(1)(A), 21 USC § 360d(c)(1)(A) (2006) (added by FDAMA § 204(a), 111 Stat. at 2335-36).

²¹⁸FFDCA § 514(c)(1)(B), 21 USC § 360d(c)(1)(B) (2006) (added by FDAMA § 204(a), 111 Stat. at 2335-36).

proved alternatives, or whose availability would be in the best interest of patients.²¹⁹

Certainty of Review Timeframes

Congress reinforced the requirement that 510(k) submissions be acted on within 90 days of filing.²²⁰

Modifications of Postmarketing Controls

For the first time, Congress substantially aligned postmarket controls to device classifications in 1997. Perhaps unwittingly, that restructuring may have discouraged the FDA from down-classifying device types from Class II to Class I. Doing so would have sharply reduced the potential regulatory tools available to the agency in the future if a problem with the down-classified type of device emerged.

Limiting Device Tracking to Class II and Class III Devices

The 1997 law limited the FDA's authority to require device tracking to Class II or Class III devices whose failure would be reasonably likely to have serious adverse health consequences or that are intended to be implanted for more than 1 year or are life-sustaining or life-supporting and used outside a device-user facility.²²¹

Limiting Postmarket Surveillance Requirements to Class II and Class III Devices

Congress also restricted the FDA's power to order postmarket surveillance for devices to those in Class II or Class III whose failure would be reasonably likely to have serious adverse health consequences or that are intended to be implanted for more than 1 year or are life-sustaining or life-supporting and used outside a device-user facility.²²²

²¹⁹FFDCA § 515(d)(5), 21 USC § 360e(d)(5) (2006) (added by FDAMA § 202, 111 Stat. at 2334).

²²⁰FFDCA § 510(n), 21 USC § 360(n) (2006) (added by FDAMA § 209(a), 111 Stat. at 2341).

²²¹FFDCA § 519(e), 21 USC § 360i(e) (2006) (revised by FDAMA § 211, 111 Stat. at 2345-46).

²²²FFDCA § 522, 21 USC § 360l (2006) (revised by § 212, 111 Stat. at 2346).

Changes in Requirements for Reporting Adverse Events Associated with Medical Devices

The 1997 law eliminated mandatory reporting by distributors of medical devices.²²³ It also eased reporting requirements for device-user facilities and directed the FDA to establish a sentinel reporting system, relying on a representative sample of all device-user facilities, to collect information on device-related deaths and serious illness or injuries.²²⁴

1997–2009 DEVELOPMENTS

The Medical Device User Fee and Modernization Act of 2002

The Medical Device User Fee and Modernization Act had two major components but did not make any fundamental change in the general regulatory scheme created by the prior enactments. The first established a “user-fee” program whereby medical-device manufacturers paid fees for some applications, reports, and supplements sent to the FDA for evaluation and imposed performance goals for the FDA in reviewing these applications. The user-fee program was to operate for 5 years. “The fees are based on the relative level of effort required for reviews.”²²⁵ It is interesting to observe, therefore, that Congress fixed the effort required for a 510(k) review at 1.75% of that for a PMA review.²²⁶ That ratio is not substantially different from the one described by the FDA in 1987, when the agency said that the average PMA review took 1,200 hours but the average 510(k) review took only 20 hours (1.67%).²²⁷ Congress also authorized specific federal appropriations for the FDA to conduct safety surveillance of marketed medical devices.

The other part of the legislation consisted of targeted changes to reduce regulatory burdens and agency workload. For example, Congress

- Created a system whereby people other than federal employees could be accredited to conduct inspections of manufacturers of Class II and Class III devices.²²⁸
- Permitted labeling for prescription devices intended for use in health-

²²³FFDCA § 519(a), 21 USC § 360i(a) (2006) (revised by FDAMA § 213(a), 111 Stat. at 2346-47).

²²⁴FFDCA § 519(b), 21 USC § 360i(b) (2006) (revised by FDAMA § 213(c), 111 Stat. at 2347-48).

²²⁵H.R. REP. NO. 107-728, pt. 1, at 24 (2002).

²²⁶*Id.* at 24 table 1.1.

²²⁷S. REP. NO. 101-513, at 15; *Medical Devices and Drug Issues: Hearings Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 100th Cong. 384 (1987).

²²⁸FFDCA § 704(f)–(g), 21 USC § 374(f) (2006) (added by the Medical Device User Fee and

care facilities to be provided solely by electronic means (for example, over the Internet).²²⁹

- Directed that registration of device manufacturers and listing of marketed devices be converted to electronic filings as soon as feasible.²³⁰
- Required the FDA to undertake “modular review” of discrete portions of a PMA before the filing of a complete PMA so that questions on these portions could be resolved early and the number of issues that might delay final approval could be reduced.²³¹

The Medical Devices Technical Corrections Act of 2004

The Medical Devices Technical Corrections Act of 2004 made a series of minor corrections in elements of the 2002 law but did not modify the substance of that act or the overall system for regulating medical devices.²³²

The Medical Device User Fee Stabilization Act of 2005

The Medical Device User Fee Stabilization Act of 2005 was intended to address gaps in expected revenues in the 2002 user-fee legislation.²³³

The Food and Drug Administration Amendments Act of 2007

The most recent device-related legislation renewed the user-fee system but did not alter the regulatory scheme in any meaningful way.²³⁴

January 2009 Government Accountability Office Report

The 2007 amendments directed GAO to examine which premarket review process—510(k) or PMA—the FDA used to review selected types of devices from FY 2003 through FY 2007.²³⁵ It found that the agency had reviewed 13,199 submissions for Class I and Class II devices through the

Modernization Act of 2002, Pub. L. No. 107-250, § 201, 116 Stat. 1588, 1602-09 (2002) [hereinafter, MDUFMA]).

²²⁹FFDCA § 502(f), 21 USC § 352(f) (2006) (added by MDUFMA § 206, 116 Stat. at 1613).

²³⁰FFDCA § 510(p), 21 USC § 360(p) (2006) (added by MDUFMA § 207, 116 Stat. at 1613).

²³¹FFDCA § 515(c)(3), 21 USC § 360e(c)(3) (2006) (added by MDUFMA § 209, 116 Stat. at 1613).

²³²Medical Devices Technical Corrections Act, Pub. L. No. 108-214, 118 Stat. 572 (2004).

²³³Medical Device User Fee Stabilization Act of 2005, Pub. L. No. 109-43, 119 Stat. 439 (2005).

²³⁴Medical Device User Fee Amendments of 2007, Title II of the Food and Drug Administration Amendments Act, Pub. L. No. 110-85, 121 Stat. 823, 842 (2007).

²³⁵Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85 § 225, 121 Stat. 823, 854 (2007).

510(k) clearance process and cleared 90% for marketing. In addition, 342 submissions under 510(k) were for Class III devices, of which 67% were cleared. Finally, 217 original PMA applications and 784 supplemental PMA applications for Class III devices had been reviewed, of which 78% were approved. As of October 2008, 20 types of Class III devices could still be cleared through the 510(k) clearance process (GAO, 2009b, pp. 6, 17).²³⁶ GAO observed that, relative to the PMA process, the 510(k) review system is generally less stringent, faster, and less expensive. With respect to stringency, GAO said:

For most 510(k) submissions, clinical data are not required and substantial equivalence will normally be determined based on comparative device descriptions, including performance data. In contrast, in order to meet the PMA approval requirement of providing reasonable assurance that a new device is safe and effective, most original PMAs and some PMA supplements require clinical data. In addition, other aspects of FDA's premarket review are [also] less stringent. . . . For example, FDA generally does not inspect manufacturing establishments as part of the 510(k) premarket review process—the 510(k) review process focuses primarily on the end product of the manufacturing process rather than the manufacturing process itself. In contrast, the agency does inspect manufacturing establishment as part of its review of original PMA submissions [Footnotes omitted]. (GAO, 2009b, pp. 14–15)

The estimated average cost to the FDA for reviewing a 510(k) in FY 2005 was about \$18,200, compared with \$870,000 for a PMA (GAO, 2009b, pp. 14–15). That is a ratio of roughly 2.09%, not far from the 1987 ratio of 1.67% based on the estimated numbers of staff-hours to review a 510(k) (20) and a PMA (1,200). As mentioned before, the FDA does not believe that the 1987 estimates are reliable today (Desjardins, 2011).

October 2009 Department of Health and Human Services Inspector General Report

The HHS inspector general conducted a review of medical-device adverse-event reporting in 2003–2007 to assess the extent of reporting, the extent of compliance with reporting requirements by manufacturers and user facilities, and the use of these reports by the FDA to identify and address safety concerns (OIG, 2009). Among the findings, the FDA received twice as many reports in 2007 as in 2003; most manufacturer reports were on time, but many of the user-facility reports and those from manufacturers that were supposed to be filed in 5 days because of their seriousness were

²³⁶The FDA reports that as of 2009, 26 types of Class III devices could still be cleared through the 510(k) clearance process (FDA, 2011).

late; and CDRH was not using the reports in a systematic manner to identify and address safety issues (OIG, 2009, ii). On the last point, the inspector general made a number of specific observations, which echoed the GAO report of 1997 (OIG, 2009, pp. ii–iii):

- Analysts did not adequately document information regarding their reviews, so it was difficult to trace a response to an individual event.
- The FDA could not link postmarket surveillance activities to particular events.
- The agency lacked a system to document when adverse-event reports resulted in onsite inspections.
- There was a serious delay between receipt of reports and when they are substantively reviewed in the FDA.
- The FDA rarely acted when manufacturers or user facilities submitted late reports.
- The agency made little use of annual reports from user facilities.

The inspector general recommended that the FDA develop a protocol for reviewing adverse-event reports, including documentation requirements, provisions for timely review of high-priority reports, and follow-up with late reporters (OIG, 2009, pp. iii–iv).

CLOSING OBSERVATIONS

This chronologic inventory has attempted to identify materials bearing on six issues relevant to the consideration of the effectiveness of the 510(k) system:

- Whether a 510(k) determination that a new device is substantially equivalent to a predicate device is a finding that the new device is safe and effective.
- Whether 510(k) decisions made over the past 35 years are of sufficient quality and reliability to serve as predicates for future 510(k) actions.
- Whether each type of Class II device must be subject to special controls to provide reasonable assurance of the safety and effectiveness of devices of that type.
- Whether procedural requirements have unduly interfered with the FDA's ability to execute its duties.
- Whether the postmarketing system for detecting device-related adverse medical events or failures of effectiveness can be relied on in

drawing conclusions about the overall effectiveness of the regulatory scheme.

- Whether the appropriate balance has been found between premarket clearance and postmarketing controls.

Those issues have repeatedly been identified and discussed by congressional bodies, by HHS, by the courts, and by the FDA itself. The committee's conclusions and recommendations on those questions are set forth in Chapter 7 of the present report.

As a general observation, however, it is clear that the consistent lack of adequate resources can undo much of what Congress envisions when it enacts a regulatory law. The experience of the FDA in implementing the medical-device law is an excellent example. Congress set forth an elaborate regulatory scheme with classification of all devices, PMA for novel and high-risk devices, performance standards and special controls for medium-risk devices, a preclearance mechanism for medium-risk and low-risk devices, surveillance for adverse events related to devices in use, and numerous powers by which the FDA could act to address problems with marketed devices. Congress never, however, provided the funds to perform all those tasks in strict accordance with the statute and within the timeframes that Congress desired. The agency later concluded that reviewing PMAs and reclassifying Class III devices were too expensive, as would establishing performance standards have been. The FDA evolved the 510(k) mechanism into an alternative to those options.

The system that the FDA operates today reflects cumulative administrative interpretations of the laws enacted by Congress in 1976, 1990, and 1997, informed by internal and external criticisms, advanced by technologic processes, and adjusted to the political and budget priorities of 6 presidential administrations and 18 Congresses. But it is not necessarily the system that would be designed if Congress started over today in recognition of the likelihood of the FDA's resources for the foreseeable future.

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B

Committee Biographies

David R. Challoner, MD (*Chair*), is vice president for health affairs emeritus of the University of Florida. He previously served as dean and professor of medicine of the St. Louis University School of Medicine from 1975 to 1982 and as the University of Florida vice president for health affairs and chairman of the Board of Directors of Shands Health Care from 1982 to 1998. He is a member of the Institute of Medicine (IOM), in which he served as chairman of the Membership Committee, as a member of the Governing Council, and as foreign secretary from 1998 to 2006. He was instrumental in the founding of the InterAcademy Medical Panel, the first global organization of the world's medical academies, and served as its cochair. His science-policy positions include appointment by President Reagan to chair the President's Committee on the National Medal of Science from 1988 to 1990. He served on the Advisory Committee to the director of the National Institutes of Health; on the National Academies' umbrella Committee on Science, Engineering, and Public Policy; and on the Governing Board of the National Research Council. He was the recipient of the American Medical Association's Dr. William Beaumont Award in 1982 for "outstanding contributions to the profession of medicine by a physician under the age of 50" and of IOM's McDermott Medal in 2010 for distinguished service to IOM and the National Academies. Dr. Challoner received his MD cum laude from Harvard Medical School.

Gary S. Dorfman, MD, is vice-chairman for research and a professor in the Department of Diagnostic Radiology at Weill Cornell Medical College. He has served as the president of the New England Society of Cardiovascular

and Interventional Radiology, the Radiological Society of Rhode Island, and the Cardiovascular and Interventional Radiology Society (now the Society of Interventional Radiology) and as the chairman of the Board of the Cardiovascular and Interventional Radiology Research and Educational Foundation. Dr. Dorfman has also served as acting chief of the Image Guided Intervention Branch and special assistant to the associate director of the National Cancer Institute (NCI) Cancer Imaging Program. He is a fellow of the Society of Interventional Radiology, the American Heart Association's Council on Cardiovascular Radiology, the American College of Angiology, and the American College of Radiology. He is on the faculty of the Radiological Society of North America (RSNA) Clinical Trials Methodology Workshop; is chair of the Clinical and Transitional Science Awards Imaging Working Group's Clinical Trials Committee, in which capacity he leads the Uniform Protocols for Imaging in Clinical Trials Process; is the organizing faculty member for the RSNA Interventional Oncology Symposium; and was a member of NCI's Translational Research Working Group and its Writing Committee. Dr. Dorfman received his MD from the Yale University School of Medicine.

Barbara Evans, PhD, JD, LLM, is a law professor, codirector of the Health Law and Policy Institute, and director of the Center on Biotechnology and Law at the University of Houston Law Center. She is an adjunct research professor of clinical pharmacology at the Indiana University School of Medicine and an affiliated investigator of the Indiana University Center for Bioethics. Earlier in her career, she was a partner in the international regulatory practice of a large New York law firm and advised clients on US medical-device regulatory matters. She holds a bachelor's degree in electrical engineering from the University of Texas at Austin, an MS in applied earth science and a PhD in earth sciences from Stanford University, a JD from Yale Law School, and an LLM in health law from the University of Houston, and she completed a postdoctoral fellowship in clinical ethics at the M.D. Anderson Cancer Center.

Lazar J. Greenfield, MD, retired as chairman of the Department of Surgery and surgeon-in-chief of University of Michigan Hospitals in 2002 and became interim executive vice-president for medical affairs. He serves as editor-in-chief of *Surgery News* and associate editor of *e.FACS*, the Web portal of the American College of Surgeons. He is a member of the Institute of Medicine. Dr. Greenfield is board-certified in general, vascular, and cardiothoracic surgery. He has been listed in *Best Doctors in America* since 1992. Dr. Greenfield is the inventor of the Greenfield vena caval filter for protection against pulmonary embolism, for which he received the

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