

GAO

Report to the Chairman, Committee on
Labor and Human Resources, U.S.
Senate

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MEDICAL DEVICE REGULATION

Too Early to Assess European System's Value as Model for FDA





United States
General Accounting Office
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**Health, Education, and
Human Services Division**

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The Honorable Nancy L. Kassebaum
Chairman, Committee on Labor
and Human Resources
United States Senate

Dear Madam Chairman:

Medical devices play a vital role in promoting public health and diagnosing and treating illness. The Food and Drug Administration (FDA) is the arm of the U.S. Public Health Service responsible for ensuring that the American public has access to devices that are safe and effective. Members of Congress, representatives of the medical device industry, and others have expressed concern that FDA takes too long to review and approve new medical devices, thus delaying the public's access to useful, and possibly life-saving, medical care.¹

In 1993, the European Union (EU) began to implement a new system to regulate medical devices—a system whose approach differs from that of the United States.² Many critics of FDA have suggested that the new EU device review system offers a model that would enable innovative technology to reach U.S. consumers more quickly without increasing risks to the public's health.

You asked us to examine both FDA's and the EU's device review systems. The objectives of our review were to (1) identify key differences between the U.S. and EU systems for reviewing medical devices; (2) compare outputs of the two systems, such as review time, if data were available; and (3) examine the feasibility of FDA's adopting features of the EU system. In preparing this report, we met with and analyzed data provided by FDA officials; EU, United Kingdom (UK), and German government officials; and representatives of private review bodies and the medical devices industry in the United States, Germany, and the UK. We conducted field work in

¹See U.S. Congress, House of Representatives, Committee on Commerce, Subcommittee on Oversight and Investigations, *A Consumer's Perspective on Medical Devices*. Hearings: March 30, 1995, 104 Cong., 1st sess. (Washington, D.C.: U.S. Government Printing Office, 1995); and The Wilkerson Group, Inc., *Forces Reshaping the Performance and Contribution of the U.S. Medical Device Industry*, prepared for the Health Industry Manufacturers Association (New York: June 1995), p. xxvii.

²The 15 member states of the EU, formerly the European Economic Community, are the United Kingdom, Ireland, Denmark, Greece, Germany, France, Italy, Spain, Portugal, Belgium, Luxembourg, The Netherlands, Sweden, Finland, and Austria. The medical device regulatory system we will discuss in this report is being implemented in the European Economic Area, which was established in January 1994 and consists of the EU member states plus Norway, Iceland, and Liechtenstein. We will refer to the system as the EU system throughout the report.

Germany and the UK because those countries were among the most advanced in implementing the EU system. We conducted our review from March through December 1995 in accordance with generally accepted government auditing standards. For a complete description of our scope and methodology, see appendix I.

Results in Brief

The EU system for regulating medical devices is still evolving, with major aspects of the system not yet fully in place. Drawing a meaningful comparison between the EU and FDA is therefore not possible at this time. The ability of the EU system to ensure the safety of medical devices and provide an efficient review process will become more evident after the system accumulates several years of experience.

However, it is possible to compare certain features of the medical device regulatory systems in the United States and the EU. For example, the two systems operate within different legal and policy contexts. U.S. law gives responsibility for device regulation to the Food and Drug Administration, an agency of the Public Health Service. FDA's charge is a public health mandate: to ensure that devices that reach the U.S. public are safe and effective. The EU system's mission is twofold. It is designed not only to ensure that devices are safe but also to facilitate EU-wide trade by creating a single review process that permits devices to be marketed in all member states.

Key differences between the two systems include the roles of public and private sector bodies and the relationships among the principal parties involved in device production and regulation. In the United States the government alone regulates devices. Under the EU system, both governmental and private organizations—called “notified bodies”—review and approve medium- and high-risk devices; most notified bodies (NB) are private. Manufacturers contract with the NB of their choice to conduct assessments of devices they would like to market. Reviewers in both the United States and the EU are subject to conflict-of-interest rules, but the rules that govern FDA reviewers are more comprehensive than those that apply to NB employees.

The systems' criteria for device approval and clearance also differ. In the EU, devices are generally evaluated for safety and their ability to perform as the manufacturer intended. The criteria FDA must use are safety and effectiveness. Effectiveness includes the additional standard of providing benefit to patients.

Meaningful comparison of the length of review time in the United States and the EU is not possible because there are no data documenting review times under the new EU system comparable to data describing FDA's experience. FDA is attempting to better manage its review process by experimenting with different procedures. Recent trends in FDA review time vary by type of review but generally show improvement for applications submitted in fiscal year 1994.

Background

Medical devices encompass a wide array of products with myriad uses. A medical device can be any product used to cure, prevent, diagnose, or treat illness, provided that its principal intended purposes are not achieved primarily by chemical or metabolic action, as would be the case with a pharmaceutical. Devices range in complexity from simple tongue depressors to heart pacemakers and sophisticated imaging systems. There are more than 100,000 products in over 1,700 categories, and they cover a wide spectrum of risk. The U.S. medical device industry grew from 5,900 firms in 1980 to 16,900 firms in 1995. U.S. consumption of medical devices exceeded \$40 billion in 1994.

Food and Drug Administration

The 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic (FFD&C) Act gave FDA expanded responsibility for regulating medical devices in the United States. FDA's regulatory responsibilities have three components: (1) approving new medical devices' entry into the market; (2) monitoring device manufacturers' compliance with FDA laws and regulations, including the good manufacturing practices (GMP) regulation to ensure continued quality control; and (3) operating a postmarketing surveillance (PMS) system to gather information about problems that could necessitate withdrawing a device from the market or taking other actions.³

The Office of Device Evaluation within FDA's Center for Devices and Radiological Health is responsible for the evaluation of medical device applications. During fiscal year 1994, the Office of Device Evaluation

³The GMP regulation, promulgated under section 520 of the FFD&C Act, requires that domestic or foreign manufacturers of medical devices intended for commercial distribution in the United States have a quality assurance program. The regulation requires that various specifications and controls be established for devices and that finished devices meet these specifications. The PMS system under the Safe Medical Devices Act of 1990 requires manufacturers, distributors, and user facilities to submit medical device reports to FDA whenever a device has caused or contributed to serious adverse incidents. In addition, manufacturers are required to conduct studies to gather data on the safety and effectiveness of certain devices designated by FDA.

received 16,905 submissions for review, of which it classified 10,293 as major submissions.

The 1976 amendments established a three-part classification system for devices, based on the device's level of risk and the extent of control necessary to ensure the safety and effectiveness of the device. Most medical devices are Class I or Class II (low and medium risk) and reach the market through FDA's premarket notification—or 510(k)—process.⁴ Under its 510(k) authority, FDA may grant clearance for the marketing of devices if it determines that they are substantially equivalent to certain devices already on the market—called predicate devices. Once FDA has made that determination, a manufacturer can begin to market the new device.

High-risk, or Class III, devices enter the market through the premarket approval (PMA) process.⁵ A PMA review is more stringent and typically longer than a 510(k) review. If a manufacturer needs to test a new device in human subjects before applying for marketing approval or clearance, and if the device presents a significant health risk to subjects, the manufacturer applies to FDA for an Investigational Device Exemption (IDE) to allow use of the device in clinical studies. See appendix II for a more detailed discussion of FDA's review processes.

The U.S. medical device industry values FDA's "stamp of approval" but has leveled several criticisms against FDA. The industry contends that FDA takes too long to review applications and that review time increased drastically in the early 1990s. Manufacturers maintain that FDA's review process is unpredictable and burdensome, particularly with regard to the amount and types of data they must submit. Additionally, the industry has stated that FDA is not always reasonable when it requires randomized human clinical trials to demonstrate that a device is safe and effective.⁶

⁴Premarket notification is commonly called 510(k) in reference to section 510(k) of the FFD&C Act.

⁵A PMA is a premarket approval application for a Class III medical device. Another type of application is the PMA supplement, an abbreviated application made subsequent to an approved PMA for approval of a change or modification in a Class III medical device.

⁶The medical device industry was also critical of the Health Care Financing Administration's (HCFA) policy of refusing to allow Medicare coverage for certain procedures and devices undergoing clinical trials. In September 1995, HCFA announced that it would modify this policy and that FDA would assist in identifying nonexperimental investigational devices for which the underlying questions of safety and effectiveness have been resolved, and that therefore may be eligible for Medicare reimbursement.

European Union

In 1990, the EU began to adopt a series of three directives to regulate the safety and marketing of medical devices throughout the EU. The directives specify roles in the device regulatory system for the European Commission;⁷ the governments of member states; and review and approval organizations called notified bodies, which are often private entities. When this system is fully in place in several years, every medical device marketed in the EU will have to carry a “CE” mark, indicating that it meets common standards of performance and safety, known as essential requirements.⁸ Devices carrying the CE mark can be marketed throughout the EU.

The first EU directive, for active implantable devices, covers powered devices that remain in the human body, such as heart pacemakers. It first took effect on January 1, 1993. During a 2-year transitional period, member states could continue to implement their national laws governing these devices, and manufacturers had the choice of either seeking approval to market a device in individual countries under each country’s laws or following the procedures that would allow the device to carry the CE mark and be marketed throughout the EU. As of January 1, 1995, all active implantable devices were subject to the new EU system alone.

The second directive, known as the Medical Devices Directive (MDD), covers most other medical devices, ranging from bandages to hip prostheses. The MDD took effect on January 1, 1995, and its transitional period will last until June 13, 1998. The third directive, covering in vitro diagnostic medical devices, such as blood grouping reagents and pregnancy test kits, is under development and will not take effect until at least 1998.

Device Review Has Different Goals in United States and European Union

The U.S. and EU medical device regulatory systems share the goal of protecting public health, but the EU system has the additional goal of facilitating EU-wide trade. Another distinction between the two systems pertains to the criteria for reviewing devices. Devices marketed in the EU are reviewed for safety and performing as the manufacturer intended; devices marketed in the United States are reviewed for safety and

⁷The European Commission is the executive branch of the EU and has 22 Directorates General to carry out EU legislation. Additionally, the Commission has exclusive authority to initiate EU legislation, which must be approved by the European Council (the principal law-making body) and often the EU Parliament.

⁸Custom-made medical devices and devices intended for investigational use are not required to carry the CE mark but do have to meet the essential requirements for safety.

effectiveness. Effectiveness includes the additional standard of providing benefit to patients.

EU System Intended to Promote Trade and Public Health

One goal of the EU medical device review system is to lower trade barriers and achieve a single market throughout the EU by harmonizing member states' regulatory controls. At the EU level, the Directorate General for Industry is responsible for implementing the medical device directives. The directives specify that a member state may not create obstacles to the marketing of a CE-marked device within its territory.

The other goal of the EU system is to protect public health. Medical devices that circulate in the EU must meet the medical device directives' essential requirements, the first one being that devices will not compromise the health and safety of patients. The responsibility for enforcing the national regulations that implement the directives in the member states lies with each country's Department of Health. Before the inception of the EU system, the level of regulation in member states varied widely, and in some countries most medical devices were not regulated at all. Therefore, although the system was created within the context of encouraging trade, in many European countries the directives will increase the level of medical device safety regulation.

The U.S. medical device regulatory system exists within a public health context. FDA's mandate is to ensure that devices that reach the public are safe and effective. The agency has limited statutory responsibility to promote trade.⁹

⁹The Office of International Relations in FDA was established by statute in 1990 to facilitate commerce by, for example, encouraging mutual recognition of good manufacturing practices, testing protocols, and other regulations. FDA has a Division of Small Manufacturers Assistance, as mandated by the 1976 Medical Device Amendments, to provide technical assistance and regulatory guidance to manufacturers to help them comply with FDA requirements for medical devices. Additionally, the Secretary of Health and Human Services, in establishing effective dates for medical device performance standards, must attempt to minimize losses to domestic and international trade.

Devices Must Meet Different Criteria in European Union and United States

Devices marketed in the EU under the new regulatory system must conform to the essential requirements contained in the applicable medical device directive.¹⁰ Because the directives cover a wide range of products, the essential requirements provide broad targets for manufacturers to meet. The essential requirements are divided into two sections. First, the general requirements state that devices must be designed and manufactured in a way that will not compromise patient health and safety and that devices must perform as the manufacturer intended. Second, the design and construction requirements cover topics such as chemical, physical, and biological properties; labeling; radiation safety; and accuracy of measuring functions.

The EU system relies greatly on recognized performance standards, which can be international, European, or national.¹¹ Demonstrating that a device meets such standards is voluntary, but this is an acceptable—and often convenient—way to demonstrate that a device complies with the essential requirements.¹²

In reviewing medical device applications FDA uses the two criteria mandated by law—safety and effectiveness. For devices entering the market through the 510(k) route, the manufacturer must demonstrate comparative safety and effectiveness, that is, the new device is as safe and effective as the legally marketed predicate device. In evaluating the safety and effectiveness of a Class III device through the PMA route, FDA must determine that the application demonstrates a reasonable assurance that the device is safe and effective.

¹⁰Medical device regulation in the EU follows the approach to harmonized regulation that the EU is applying in many different regulatory arenas for a variety of products. The strategy is to achieve harmonization through essential requirements that are both general and mandatory, and that are complemented by European standards that are both detailed and voluntary. See Linda R. Horton, "Medical Device Regulation in the European Union," *Food and Drug Law Journal*, Vol. 50 (1995), pp. 461-476.

¹¹There are three levels of performance standards. Level I are global, or horizontal, standards, which are common to all medical devices and relate to broad dimensions like electromagnetic compatibility and sterilization processes. Level II, or vertical, standards apply to a family of devices, such as all implantables (for example, pacemakers and artificial joints), and relate to subjects like materials and toxicity. Level III standards are product-specific (for example, for heart valves). For additional information on standards, see *Medical Technology: Quality Assurance Systems and Global Markets* (GAO/PEMD-93-15, Aug. 18, 1993), pp. 27-28.

¹²The European Commission has mandated European standards organizations, such as the European Committee for Standardization (CEN), to prepare harmonized European standards for medical devices that will enable manufacturers to show that their products comply with the essential requirements. A European Commission official told us that the Commission expects to develop 250 standards within a few years. Manufacturers may use national or international standards when there is no European standard.

To satisfy the effectiveness requirement, a device must provide beneficial therapeutic results in a significant portion of the target patient population.¹³ The U.S. criterion of effectiveness encompasses more than the European criterion of performing as the manufacturer intended; it requires the device to benefit certain patients. For example, to market an excimer laser in the United States, the manufacturer must demonstrate not only that the laser can cut tissue from the patient's cornea, but also that the laser procedure lessens or eliminates the patient's nearsightedness. In the EU, if the manufacturer specified that the purpose of the device was to eliminate a patient's nearsightedness, it would have to demonstrate the validity of that claim. However, if the claim was restricted to the device's ability to remove tissue in a particular way, judgment of the appropriate use of the device would be left to clinicians.

In evaluating effectiveness, FDA generally reviews an individual device on its own merits. In certain situations, however, reviewers consider whether a new device is potentially less effective than available alternative therapies. FDA's position is that the agency evaluates comparative effectiveness only when a less effective device could present a danger to the public, that is, when a device is designed to treat a disease that (1) is either life-threatening or capable of causing irreversible morbidity, or (2) is a contagious illness that poses serious consequences to the health of others.

United States and EU Review Systems Structured Differently

The EU gives major regulatory responsibilities to public and private bodies; in contrast FDA has sole responsibility in the United States. Both systems link the level of medical device review to the degree of control needed to ensure device safety. However, the two systems use different procedures to reach approval or clearance decisions.

Public Agencies and Private Notified Bodies Have Roles in EU Device Regulation

Governmental and private organizations both perform major functions in the EU system for regulating medical devices. Each member state designates a competent authority, usually in the Department of Health, which is responsible for implementing and enforcing the medical device directives in that country.¹⁴ The competent authority ensures that the

¹³Effectiveness means the same thing in the 510(k) and PMA processes, but is largely presumed for 510(k)s and must be proven for PMAs.

¹⁴The structure of Germany's competent authority is different from that of other countries because the central government has delegated some medical device functions to the 16 state governments, or Bundesländer. As a result, the Ministry of Health and agencies at the state level share responsibilities that in other countries are generally performed by only one central agency.

directives are incorporated into national law, approves clinical investigations of devices, and operates the country's reporting system for adverse incidents. Additionally, the medical device directives contain a safeguard clause. This clause gives the competent authority the power to withdraw an unsafe device from the market; the competent authority can be overruled by the European Commission after consultation among all of the parties concerned. (See app. III for a more detailed discussion of the safeguard clause.) The competent authority also serves as the country's liaison with the European Commission and other member states.

One of the most important responsibilities of the competent authority is to designate and certify the notified bodies located in that country. NBS are the organizations that perform conformity assessments on medical devices of medium or high risk that require the intervention of an independent organization prior to CE marking. The NBS determine whether a device conforms to the essential requirements in the relevant medical device directive. If the device is judged to be in conformance, the manufacturer may then place the CE mark on the product and market it throughout the European Union. NBS may be governmental or private entities, but most are private.

In making their NB designations, competent authorities consider whether organizations meet the criteria for NBS contained in the medical device directives. These criteria include standards of competence, impartiality, and confidentiality. Competent authorities may periodically audit NBS and can withdraw NB status from an organization that does not continue to meet the criteria.

The competent authority certifies that an NB is qualified to evaluate certain types of devices and to perform specific conformity assessment procedures. Some NBS have a limited certification; for example, they can evaluate only active medical devices or can perform only certain types of quality assurance reviews. Others are qualified to evaluate almost the full range of devices. If an NB is not competent to perform an assessment procedure that a device requires, it can subcontract with another NB or with another organization, such as a testing laboratory, to perform that part of the assessment.

A manufacturer may select an NB located in any member state to assess its device. This is a contractual relationship, with the manufacturer paying a fee for the NB's services. As of October 1995, there were 40 NBS throughout the EU. Germany and the UK had the largest number, 16 and 8, respectively.

Representatives of European industry groups and public and private officials in the UK and Germany told us that manufacturers consider several factors when selecting an NB. These include the NB's expertise and experience with specific devices and assessment procedures, language, cost, and whether the manufacturer has worked with the NB previously.

FDA Regulates Devices in the United States

In the United States, regulatory responsibilities rest with one government body—FDA. Currently, however, FDA is creating a pilot program to test the use of private third parties to review low- to moderate-risk devices requiring 510(k) clearance. The agency will individually review and accept third-party review organizations interested in participating in the pilot. After completing a device review, the third party will make a clearance recommendation to FDA. In contrast with the role of European NBS, the private reviewers participating in FDA's pilot program will not have authority to make clearance decisions. FDA will retain that authority and will base its decision on the third party's documented review.

Manufacturers' participation in the pilot will be voluntary; they may continue to opt for FDA review. Applicants that must submit clinical data on their devices will not be able to select third-party review; FDA has prepared a preliminary list of devices that may be included in the pilot. FDA expects that applicants that do participate will pay a fee directly to the third party to conduct the review.¹⁵ The pilot is scheduled to begin in mid-1996 and will operate for 2 years; during the second year FDA plans to evaluate the feasibility of using third parties to conduct timely and high-quality reviews of devices.

Both Systems Link Level of Review to Device Risk

Like the United States, the EU has a risk-based device classification system. The EU has four categories, however, instead of three. The manufacturer determines the appropriate class for a new device, based on classification rules in the directives. The manufacturer may also consult with the NB reviewing the device.¹⁶ In the United States, the manufacturer makes a claim regarding which class a device belongs in when it submits

¹⁵FDA does not expect to take part in determining these fees. Fees will be negotiated between the third party and the applicant.

¹⁶If the NB does not agree with the manufacturer's interpretation of the medical device directive, it will present to the competent authority the manufacturer's reasons for believing its device belongs in a different class. The competent authority can then make a decision regarding the correct device classification. The competent authority can, if necessary, ask the European Commission for a ruling. The European Commission would act in conjunction with a committee composed of experts from the member states.

an application for FDA review. FDA, however, has final authority over the classification decision. (See app. III for a more detailed discussion of the EU classification system and app. II for a more detailed discussion of the FDA classification system.)

Just as every device released in the United States must demonstrate safety and effectiveness, every device in the EU, no matter what its class, must comply with the essential requirements. In both systems, the purpose of classifying devices is to dictate the level of control the system exerts to ensure that devices comply with the respective requirements.¹⁷

The EU directives set out a complex array of assessment procedures that manufacturers must follow to demonstrate that a device conforms to the essential requirements. A device's class determines the type of conformity assessment review the device must undergo, but the manufacturer is usually permitted to choose an assessment route from at least two options—often involving two general approaches. One approach is a review of the full quality assurance (QA) system that governs every phase of the manufacture of a device, from design through shipping.¹⁸ Officials of a German NB told us that one goal of a full QA review is to ensure that the manufacturer has written quality control procedures for every one of these phases and that these procedures are followed.¹⁹ NB reviewers conduct on-site inspections as part of this process.

The other approach consists of two components. The first is a procedure called a type examination, in which the NB physically tests a prototype of the device to determine if it meets certain standards. The type examination component is paired with a limited QA review focused only on the production phase of manufacture. This review is intended to ensure the consistency of product quality. We refer to this overall approach as the type examination route. Appendix III contains a more detailed description

¹⁷Individual devices or device categories may not be subject to the same level of control in the U.S. and EU systems.

¹⁸A manufacturer choosing the full QA system route for a Class III device is also required to submit a design dossier for the NB's review. The dossier may include specifications and performance data of the product as claimed; risk analysis, including risk control methods; electrical/mechanical/chemical constructional data, including drawings; design verification documents; and, when relevant, clinical investigation data.

¹⁹The phases involved in producing a new device for the market include a feasibility phase; the design phase, which results in a written definition of the device; design verification, which involves creating prototypes; mass production; and full market release. At each of these phases the manufacturer must ensure that it has defined the requirements for completing that phase and that the "deliverable" for that phase—be it a product design or a packaged device—is verified by qualified staff.

of the different routes of conformity assessment and the assessment requirements for different device classes.

The EU system includes both of these device approval routes as a compromise between member states that tended to rely on one approach or the other. For example, in the UK a voluntary oversight system had emphasized full QA system review, while the type examination approach had prevailed in Germany's regulatory system.

Both the EU and U.S. systems minimize oversight for the devices considered least risky. For EU Class I devices that do not involve a measuring function or sterile products, manufacturers may simply furnish a declaration that the device conforms to the essential requirements and maintain technical documentation that would permit review of the device. There is no NB review, but the manufacturer must register such devices with the competent authority in the country of the manufacturer's place of business. In the United States, FDA exempts selected low-risk devices from premarket notification requirements. Manufacturers must still register their devices with FDA and must comply with GMP rules.

Most new U.S. devices fall into Class I or Class II and are evaluated for substantial equivalence to devices already on the market. FDA determines whether a device has the same intended use and same technological characteristics as a predicate device by reviewing a 510(k) application submission. If a new device has the same intended use and technological characteristics, FDA deems it substantially equivalent to a predicate device and allows the device to be marketed. Also, if a device has new technological characteristics and FDA determines that they do not raise different questions of safety or effectiveness, FDA will find the device to be substantially equivalent. If the device has new technological characteristics and raises different questions of safety and effectiveness, the device will be found not substantially equivalent. The manufacturer can then seek approval for it through the premarket approval process.

FDA requires a PMA review for most Class III devices. This is a more rigorous review because of the device's inherent high risk or lack of established safety and effectiveness information. A multidisciplinary staff at FDA evaluates the PMA application. Nonclinical studies that the team reviews may include microbiological, toxicological, immunological, biocompatibility, engineering (for example, stress, wear, fatigue), and other laboratory or animal tests as appropriate. The team also reviews the results of any clinical investigations involving human subjects. Generally,

FDA evaluates a manufacturer's tests and does not perform its own tests on products. For a small portion of PMA reviews, FDA reviewers seek advice from an advisory panel of clinical scientists in specific medical specialties and representatives of industry and consumer groups.²⁰

U.S. device manufacturers have expressed concern that FDA asks them to submit an excessive amount of data during the 510(k) review process. The director of FDA's Office of Device Evaluation told us that FDA requires only what is necessary to establish that a device is as safe and effective as its predicate. She also told us that FDA has chosen to interpret the 510(k) requirements so that more devices can go through that review process rather than the longer PMA process. As a result, the agency needs enough data to demonstrate that those 510(k) devices meet the standard of substantial equivalence and do not raise new concerns regarding safety and effectiveness.

EU Quality Assurance Approach Does Not Examine Individual Devices

When an NB certifies a manufacturer's full QA system, the manufacturer may be able to attach the CE mark to several related products. The philosophy behind this approach is that if a company has a good design and manufacturing system, the devices it produces will be safe and perform as the manufacturer claims. Therefore, the full QA assessment route does not require the NB to conduct individual reviews of related devices that are produced under the same QA system, although the NB can do so when the situation warrants it. The certification covers the related devices, allowing the manufacturer to market all of them without going through an additional conformity assessment. Representatives of a British industry group told us that the QA approach makes it possible to continually monitor a company without testing individual items that may not be representative of the overall quality of production.

Officials who work in the EU system told us that they expect manufacturers to choose the full QA route to conformity assessment more frequently than the type examination route. This route can be particularly advantageous for larger companies. The officials believe the type examination route is more likely to appeal to smaller companies that do not produce many product lines or a company that wants to get a particular device to market before it has time to put a full QA system in place.

²⁰FDA requests panel involvement when (1) it does not have the knowledge or experience to properly evaluate safety and effectiveness, (2) the specific PMA raises a new issue best addressed by the experience of the panel, or (3) the data establishing the clinical performance of the device reveal unanticipated safety and effectiveness questions.

The kinds of standards manufacturers must meet during European QA reviews are similar to the GMP requirements in the U.S. system. (See app. II for additional information about GMP requirements.) However, in contrast to the ability of a full QA review to stand alone as a conformity assessment route for some devices in the EU, FDA never bases a 510(k) clearance or PMA approval decision solely on a GMP inspection.

Use of Clinical Trials May Expand Under EU Directives

Some U.S. medical device manufacturers have raised concerns that FDA sometimes asks that a new medical device be tested in a clinical trial when the manufacturers believe that approach is inappropriate and unwarranted. They have also asserted that clinical trials can be performed more quickly in Europe.

European officials told us that prior to the issuance of the EU medical device directives, Europe had very few requirements for clinical investigations. Under the new system, manufacturers may be required to provide clinical evidence that a device meets the essential requirements for safety; this evidence may come from either published scientific literature on similar devices or data from a clinical trial on the device under consideration. Implementation of the EU medical device directives may result in clinical trials being required more frequently than they had been in the past.

Officials from a German NB discussed with us circumstances under which they would be likely to need data from a clinical trial to evaluate a new device under the EU directives. If the device uses an accepted technology to treat a medical indication for which use of that technology is also accepted, a clinical trial would not be necessary. If both the technology and the application are novel, however, they said they would require a clinical trial. In situations where there is a mix of novel and approved device technology and medical indication, they would need to make a judgment call. They said that regardless of whether a clinical trial is necessary, clinical data, based on either previous clinical trials, scientific literature, or field experience, would have to be provided.

Although it is unclear how frequently European reviewers will ask manufacturers to perform clinical trials, FDA officials believe that clinical trials are often needed to establish the safety and effectiveness of devices undergoing PMA review. According to FDA, fewer than 10 percent of the medical device products FDA reviews under the 510(k) process require clinical trials. When FDA does require a clinical trial during a 510(k) review,

the agency is looking for clinical confirmation that a device is as safe and effective as the legally marketed predicate device.

Notified Bodies' Independence Complicated by Dual Roles

NBS carry out a regulatory function within the EU's medical device system, but the manufacturers whose devices they review are also their clients. This raises questions about the independence of the NBS. Additionally, NB employees are subject to less comprehensive conflict-of-interest rules than are FDA device reviewers.

Notified Bodies Have Client Relationship With Subjects of Review

Unlike FDA, an NB is in the complicated position of both performing a public health function—and in that capacity having to answer to a governmental competent authority—and having a client relationship with the manufacturer that has hired it to review a device. NBS have a duty to ensure that medical devices that carry the CE mark conform to the EU medical device directives' essential requirements regarding safety and performance. At the same time, however, they are in competition with each other to secure the business of manufacturers seeking assessment services.

The businesses of some NBS include consulting work as well as product reviews, which can further complicate their independence. The director of the UK competent authority told us that if an organization has a consulting arm, his agency checks to see if the consulting function is kept separate from the conformity assessment function. Only then can it be designated as an NB. An EU official told us that he believes the European Commission needs to address this problem of potential conflict of interest for NBS.

EU Reviewers Subject to Less Comprehensive Conflict-of-Interest Rules Than FDA Reviewers

The EU medical device directives require the staff of NBS to be free of all pressures and inducements, particularly financial, that might influence their judgment or the results of their reviews, especially from anyone with an interest in the outcome of the review. To meet this requirement, NBS and their personnel must comply with European standards governing potential conflicts of interest.²¹ These standards are very general. Essentially, they (1) prohibit anyone involved in product testing or accreditation from having a commercial, financial, or other interest that could affect their judgment; and (2) attempt to shield laboratory and certification personnel from control by anyone with a direct financial interest in the outcomes of testing and accreditation. Key terms in the

²¹Criteria governing these personnel are in the EN 45000 series of European standards.

standards, such as control, direct, commercial interest, and financial interest, are not defined.

Officials of NBS we visited told us that their employees are bound by international standards and that they must disclose potential conflicts of interest in connection with their assignments. One official told us that as an internal control, the staff who conduct the periodic follow-up surveillance reviews of manufacturers after the initial certification of a product or QA system are different from those who conducted the initial review.

FDA employees are subject to a more comprehensive set of rules than are NB personnel. FDA rules include a substantial list of general rules that encompass all the goals and prohibitions included in the EU rules. In addition, they include supplemental guidance on specific matters that could present conflicts of interest, for example, outside employment, stock ownership, gifts, entertainment, filing responsibilities, and political activity. The EU rules are silent on how the general rules might apply in these situations.

Information Not Available to Compare Outcomes of New EU System and a Changing FDA

The EU medical device system is new and not yet fully operational. Although FDA's system has been in place for almost 2 decades, the agency's process is in flux as managers try to respond to criticism by experimenting with streamlined procedures. It is too early to evaluate the impact of those efforts on the length of FDA's review process. At this time there are no data on the experience of the EU device review system that permit meaningful comparison with FDA.

EU Device Review System New and Still Evolving

In contrast to FDA's almost 20 years of experience in carrying out the U.S. device review program, implementation of the EU system is quite new. The only medical device directive that is fully in effect is the one for active implantable devices. The transition period for the directive that covers most devices began just 1 year ago.

The system is not yet fully in operation. For example, each competent authority is supposed to establish a system for manufacturers to report adverse incidents with devices; eventually all of these national systems will be electronically linked. The UK already had an extensive voluntary system in place that it can build on, but most countries have barely begun to develop their systems. A UK official told us it will probably be a few

years before an EU-wide system is in place. In the meantime officials are communicating by fax and letter when they identify problems.

It is too early to know how some aspects of the EU system will translate from the directives into a practical working system. For example, the various competent authorities are bound by the same criteria when designating NBS, and the various NBS—both within and across individual member states—are all supposed to use the same criteria to perform conformity assessments. At present there is no way to measure whether that consistency is occurring in practice.

European officials told us that experience levels among the competent authorities and NBS vary. For example, in countries that previously had a regulatory program in place, such as the UK and Germany, the competent authorities already had experience carrying out some of the functions the EU system requires of them. Similarly, some NBS have long histories of evaluating medical devices or QA systems, while others have considerably less experience. Even well-established NBS may have greater experience with particular conformity assessment routes or device categories. For example, NBS in the UK tend to have extensive experience performing full QA system reviews and some German NBS have extensive experience with product testing.

Results of FDA Initiatives to Reduce Review Time Not Yet Clear

Medical device manufacturers in the United States have charged that FDA takes too long to approve new medical devices and have asserted that the review process in Europe is faster. In response to criticism about the length of its device review process, FDA is attempting to better manage and streamline its system by experimenting with different review procedures. Agency officials believe these initiatives have reduced review time, but it is too early to evaluate their impact.

FDA's management actions include the May 1994 implementation of a three-tier system of review to improve management of its workload and better link the rigor of review with a device's level of risk. In addition, since December 1994, FDA has exempted close to 300 additional medical devices from premarket notification requirements and moved other devices into lower classification categories in an effort to concentrate on riskier products and reduce the regulatory burden on manufacturers.

FDA is also experimenting with an expedited review process for life-sustaining and life-saving devices under which selected applications

move to the front of the review queue. At least 40 devices had been reviewed under this process as of July 1995. Additionally, FDA is refusing to accept deficient or poorly prepared applications until manufacturers provide the information needed for review.

We recently analyzed patterns in review time for FDA device applications submitted from October 1988 to May 1995.²² Review times for 510(k) applications and PMA supplements submitted in 1994 were still higher than they were in 1990 but had decreased from 1993 levels. The trend for original PMAs was less clear, in part because FDA has not yet completed the review of a large portion of those applications.

No Comparable Data on Length of EU Review Process

The EU does not have data on the length of its review process that can be compared with the data available about FDA's experience. The EU system has been in effect for only a short time. Anecdotal information suggests review time may be shorter in the EU, but differences between the systems make it difficult to find comparable benchmarks. For example, NBS may have extensive interaction with manufacturers before the review process formally begins, and they sometimes perform preliminary reviews before beginning the official conformity assessment. This could make it difficult to identify the date on which the NB's review begins. For similar reasons of lack of comparable data, it is also difficult to compare FDA's record with the experience of individual European countries prior to initiation of the EU-wide system.

Conclusions

The EU system for regulating medical devices is not only new—it is not yet fully in place. Therefore, it is too early to evaluate its success in ensuring the safety of medical devices and bringing them to market in an efficient manner. Because the major actors in the EU system have not had sufficient time to establish a record on how they will carry out their duties, it will be some time before information is available to answer the following questions:

- How strictly will competent authorities oversee NBS, for example, will competent authorities rescind certifications of NBS if warranted?
- Will the performance of all competent authorities and NBS be of equal quality, and therefore, will public health authorities and consumers be able to have the same level of confidence in devices no matter where they are reviewed?

²²See Medical Devices: FDA Review Time (GAO/PEMD-96-2, Oct. 30, 1995).

-
- Will the full QA system and type examination conformity assessment routes both prove to be appropriate ways to regulate devices?
 - Will NBS maintain the necessary degree of independence from manufacturers who are their clients?
 - How will NBS implement requirements for clinical evidence on new devices?
 - Will an adequate postmarket surveillance system be developed?

U.S. government officials who want to consider integrating features of the EU approach into the U.S. device review system will be better able to assess the value of the EU system after it accumulates several years of experience. The U.S. medical device industry has advocated giving private third parties a role in the review of medical devices, and FDA is exploring this possibility in a pilot project. Ensuring that private reviewers have the necessary independence, requisite expertise, and sufficient resources would enhance the confidence of the Congress and the American public in the integrity of the device review process. The importance of this assurance would increase if private review organizations were given the added authority of clearing new devices for marketing.

Agency Comments

FDA and European officials reviewed a draft of this report. FDA's written comments are reproduced in appendix IV. FDA generally found the report to be accurate and complete and made a number of technical comments clarifying aspects of the agency's review processes. We incorporated these as appropriate, basing the changes in some instances on further discussions with FDA officials. We also incorporated technical clarifications on the EU system received from European officials.

In its comments, FDA stated that the EU system does not evaluate individual devices, but instead evaluates a manufacturer's quality assurance system. As we noted in the draft report, in some situations the EU system does evaluate individual devices, such as when a manufacturer chooses the type examination route of conformity assessment or when a Class III device's design dossier is reviewed.

We will distribute this report to the Secretary of Health and Human Services, the Commissioner of the Food and Drug Administration, and other interested parties.

This report was prepared under the direction of Mark V. Nadel, Associate Director for National and Public Health Issues. If you or your staff have any questions, please call me at (202) 512-7119 or Bruce D. Layton, Assistant Director, at (202) 512-6837. Other major contributors to this report include Helene F. Toiv, Claude B. Hayeck, Mary W. Freeman, Michele Grgich, and Liv Gorla.

Sincerely yours,

A handwritten signature in black ink that reads "Sarah F. Jaggar". The signature is written in a cursive style with a long, sweeping underline that extends to the left.

Sarah F. Jaggar
Director, Health Financing and
Public Health Issues

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Abbreviations

CEN	European Committee for Standardization
EU	European Union
FDA	Food and Drug Administration
FFD&C	Federal Food, Drug, and Cosmetic
GMP	good manufacturing practices
HCFA	Health Care Financing Administration
IDE	Investigational Device Exemption
IRB	institutional review board
MDD	Medical Devices Directive
NB	notified body
PMA	premarket approval
PMS	postmarketing surveillance
QA	quality assurance
SMDA 90	Safe Medical Devices Act of 1990
UK	United Kingdom

Scope and Methodology

For our review of the European Union's medical device approval process, we conducted field work in Germany and the United Kingdom. These countries were ahead of most other member states in adopting the EU regulatory system into their national laws and had greater experience with implementing the new system. Additionally, over half of the notified bodies, which review and approve medical devices under the EU system, were located in these two countries.

In Germany and the UK we interviewed government health officials responsible for medical device regulation; officials from two NBS, TÜV Product Service and the British Standards Institution; and representatives of medical device industry groups. We also interviewed EU officials and a representative of an EU-wide industry association. We reviewed EU documents governing the EU regulatory process. Several officials we interviewed reviewed a draft of this report.

We reviewed Food and Drug Administration documents and policies as well as laws and regulations governing FDA. In addition, we interviewed officials from FDA's Center for Devices and Radiological Health.

We talked with representatives of the U.S. medical device industry, including the Health Industry Manufacturers Association, the National Electrical Manufacturers Association, and the Medical Device Manufacturers Association, as well as representatives of individual device companies. We also reviewed position papers of several industry groups. We interviewed representatives of organizations with expertise on product review and certification, including officials from the U.S. Department of Commerce; Underwriters Laboratories Inc.; the American National Standards Institute; and the Emergency Care Research Institute.

We conducted our review from March through December 1995 in accordance with generally accepted government auditing standards.

Description of Selected Aspects of FDA Processes for Regulating Medical Devices

This appendix provides additional information about several features of the U.S. system for regulating medical devices and FDA review procedures.

The process of bringing a new medical device to market takes one of two routes—premarket notification or premarket approval. Most new devices are variations of already marketed devices, are classified as low to moderate risk, and reach the market through FDA’s premarket notification—or 510(k)—review process. During the 510(k) review, FDA judges whether a device is substantially equivalent to one already on the market. The premarket approval (PMA) process is reserved for high-risk devices. PMAs and PMA supplements require a more stringent FDA review, which may include the analysis of clinical data to provide a reasonable assurance of safety and effectiveness. In addition, manufacturers must comply with certain postmarket requirements such as reporting of certain device-related adverse events. In fiscal year 1994, FDA’s Office of Device Evaluation received 6,434 510(k) applications and 415 PMAs and PMA supplements.²³

Device Classes

Medical devices are grouped into three classes according to (1) the degree of potential risk and (2) the types of regulatory control needed to reasonably ensure their safety and effectiveness. Class I devices (for example, bedpans and tongue depressors) are those for which general controls provide reasonable assurances of safety and effectiveness. Class II devices (for example, syringes and hearing aids) require special controls in addition to general controls. Class III devices (for example, heart valves and pacemakers) are subject to general controls and must undergo more rigorous scientific review and approval by FDA as well.

General controls include registering device manufacturing facilities, providing FDA with regularly updated lists of marketed devices, complying with good manufacturing practices, and maintaining records and filing reports of device-related injuries and malfunctions. The Safe Medical Devices Act of 1990 (SMDA 90) revised the requirements for Class II devices, subjecting them to both general and special controls.²⁴ Special controls include performance standards, postmarketing surveillance, patient registries, and other controls as deemed necessary. Class III devices are

²³In addition, this office received about 10,000 other submissions for review. They include Investigational Device Exemption applications, PMA amendments, and 510(k) and IDE supplements.

²⁴Prior to SMDA 90, Class II devices were to be regulated by performance standards encompassed by FDA regulations. FDA has not implemented performance standards for these devices, with the exception of a number of devices that are radiation-emitting electronic products under the radiological health provisions of the Federal Food, Drug, and Cosmetic Act.

subject to the PMA process, which requires the manufacturer to present evidence, often including extensive clinical data, that there is a reasonable assurance that a device is safe and effective before placing it on the market.

Triage

To help assess the appropriate level of review for devices, the Center for Devices and Radiological Health in May 1994 introduced a three-level “triage” system that, within the existing classification system, assigns priorities for application review based upon the complexity and risk of the device. A tier I review is essentially a labeling review to ensure that the label correctly identifies the intended use of the device. Most Class I devices fall within tier I because a less rigorous scientific evaluation of these low-risk devices does not adversely affect the public health. A tier II review is a scientific and labeling review. This tier encompasses the majority of 510(k)s and select PMA supplements. A tier III review is an intensive scientific and labeling review, using a team review approach for devices utilizing new technology or having new intended uses. FDA convenes an advisory panel when it lacks the expertise to address questions of safety and effectiveness for devices placed in tier III or when it is otherwise appropriate to obtain advice on scientific matters.

Premarket Notification—510(k)s

Most new medical devices incorporate incremental changes to devices already on the market. To clear these devices for marketing, FDA determines whether they are substantially equivalent to (that is, as safe and effective as) legally marketed predicate devices.²⁵ Substantial equivalence means that a device has (1) the same intended use and same technological characteristics as the marketed device or (2) the same intended use and different technological characteristics—but is as safe and effective as the marketed device and does not raise different questions of safety and effectiveness.

FDA initially determines whether a 510(k) submission is sufficiently complete before undertaking a substantive review.²⁶ During the review, FDA determines the intended use of a device by examining the

²⁵A legally marketed predicate device is (a) a device that was legally marketed before May 28, 1976 (date of the Medical Device Amendments of 1976, which expanded FDA’s authority to regulate medical devices); (b) a Class III device that has been reclassified into Class I or II; or (c) a device that is substantially equivalent to a device placed in (a) or (b).

²⁶For example, the FDA reviewer determines whether the application contains the information required under the Federal Food, Drug, and Cosmetic Act. Also, the application should have photographs of the device as well as engineering drawings of it.

manufacturer's proposed label statements, including statements in promotional materials that describe the device and its use. To evaluate technological characteristics, FDA reviews the physical and performance characteristics of the device, such as device design, materials used, and power source. For example, in reviewing a new pacemaker lead made of polyurethane, FDA would assess performance testing information to confirm that the new lead is substantially equivalent to the predicate (or previously approved) lead. This is necessary because differences in chemical formulations of polyurethane or differences in design and assembly can affect safety and effectiveness.

In arriving at a determination, FDA reviewers may use voluntary standards and guidance about a particular device.²⁷ Reviewers also commonly used earlier agency decisions on 510(k)s for similar devices. Another resource is the files of the Center for Devices and Radiological Health, such as establishment inspection and postmarketing surveillance files. These files allow reviewers to examine the reviews of similar device types and to determine what questions, if any, were raised by FDA inspectors about a particular type of device.

During the review of a 510(k) application, the reviewer may determine that additional information about the device is necessary to complete the review. This additional information may be descriptive information and/or performance testing information. Descriptive information includes the intended use, physical composition, method of operation, specifications, and performance claims of the device. Performance testing information can be data from bench testing or from animal or clinical testing.

Upon completion of the review, the Office of Device Evaluation issues a decision letter, which is then sent to the manufacturer. The letter may contain one of the following:

- a substantially equivalent decision,
- a not substantially equivalent decision,
- a request for additional information, or
- a determination that the device is exempt from a 510(k) submission.

²⁷FDA uses a variety of voluntary standards and draft guidance against which to judge the design and performance of medical devices. Some of these voluntary standards were developed and endorsed by groups such as the Association for the Advancement of Medical Instrumentation, often with FDA assistance. In addition, FDA staff develop FDA guidance documents for their own internal use. Manufacturers use many of these FDA internal guidance documents to help ensure that they submit a complete medical device application to FDA.

Premarket Approval

As it does for 510(k)s, FDA first decides whether to accept the PMA or refuse to file it because it does not meet minimum requirements. If FDA accepts the application, a multidisciplinary staff evaluates the filed PMA. The team reviews nonclinical studies such as microbiological, toxicological, immunological, biocompatibility, animal, and engineering tests. The team also reviews the results of clinical investigations involving human subjects. During this stage, FDA prepares a critique of the scientific evidence of the safety and effectiveness of the device.

During the review, FDA may, on its own initiative or if requested by the applicant, refer the PMA to an advisory committee representing the appropriate medical field for a “panel” review. FDA will request such a review when it lacks the knowledge or experience to evaluate the safety and effectiveness questions posed by the device or when it is otherwise appropriate to obtain advice on scientific matters. Problems identified in FDA’s critique of the scientific evidence can be discussed further during advisory panel meetings. The committee submits a final report to FDA, but the agency is not bound by the committee’s recommendations.

The review team also checks the manufacturer’s compliance with the GMP regulation and makes a judgment about the quality controls used in the manufacture of a device. The purpose of the review is to ensure that the manufacturer is capable of producing devices of high quality.

At the end of the approval review stage, FDA may take one of the following actions:

- Issue an order approving the PMA.
- Issue an order denying approval.
- Send the applicant an approvable letter indicating that the FDA intends to approve the device if certain problems (for example, labeling deficiencies) are resolved.
- Send the applicant a not-approvable letter describing significant deficiencies in the application. Eventual approval is not precluded if the manufacturer provides an adequate response.

Investigational Device Exemptions

Almost all PMAs and a small subset of PMA supplements and 510(k)s require clinical trials to obtain answers to questions on safety and effectiveness. A researcher wishing to conduct a study involving human subjects to develop safety and effectiveness data for a medical device can apply to FDA for an IDE. An approved IDE application permits the use in a clinical study

of a device that would ordinarily be subject to market clearance procedures. An IDE approval is needed for a significant risk device. For a nonsignificant-risk device (for example, daily wear contact lenses) investigation, the sponsor presents the proposed study to an institutional review board (IRB) along with a report of prior investigations and the investigational plan.²⁸ If the IRB approves the investigation as a nonsignificant-risk study, the investigation is considered to have an approved IDE and can begin immediately. FDA is not involved in the approval process of the clinical study. If the IRB or FDA determines, however, that the proposed investigation involves a significant-risk device (for example, a heart valve), the sponsor must submit an IDE application to FDA.²⁹ The application must contain an investigational plan that includes such information as the purpose of the study, a written protocol, a risk analysis and description of patient selection, a description of the device, monitoring procedures, labeling, and consent materials. An IDE application may also include data on the design of the device and data from bench and animal tests.

FDA determines whether the study should be approved, considering such factors as whether the benefits of the investigation outweigh the risks and whether the proposed study is scientifically sound. The investigation can begin after the sponsor obtains both FDA and IRB approval for a significant-risk investigation. FDA conducts bioresearch monitoring inspections to help ensure that clinical investigations are conducted in accordance with study protocols and that the rights and safety of study participants are protected.

GMP Inspections

FDA determines compliance with the GMP regulation primarily through factory inspections conducted by its field staff. Section 704(a) of the FFD&C Act gives FDA authority to conduct GMP inspections of medical device manufacturers.³⁰ During these inspections, FDA investigators examine

²⁸An IRB is any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The purpose of such review is to ensure the protection of the rights and welfare of human subjects, the appropriateness of the method for securing the subjects' informed consent to participate, and the balance of risks and benefits. The board must be composed of a minimum of five members sufficiently qualified to foster a complete and adequate review of research activities commonly conducted by the institution.

²⁹FDA is the final arbiter of whether an investigation is a significant- or nonsignificant-risk study. FDA learns of IRB nonsignificant-risk decisions through various means, including bioresearch monitoring and communications from IRBs and other sources, and can overrule an IRB's decision.

³⁰Anyone who manufactures, labels, packages, imports, or stores a medical device can be inspected. A manufacturer is any person, including a repackager or relabeler, who writes specifications for, manufactures, fabricates, assembles, or processes a medical device.

facilities, records of manufacturing processes, and corrective action programs. The results provide information necessary to evaluate a firm's compliance with the medical device GMP regulation.

FDA may initiate a GMP inspection for any of several reasons. These include routine scheduling, the need to obtain data on an industry new to FDA, investigation of a consumer or trade complaint, a product defect report, an adverse reaction to a device, or a device-related death. FDA also conducts GMP inspections in conjunction with approval of products.

Postmarketing Surveillance

One key provision of the Safe Medical Devices Act of 1990 requires that manufacturers conduct postmarketing surveillance, such as studies to gather data on the safety and effectiveness of certain devices. This requirement applies to devices that (1) are permanent implants, the failure of which may cause serious adverse health consequences or death; (2) are intended for use in supporting or sustaining human life; or (3) present a potential serious risk to human health. FDA also has discretion to require postmarketing surveillance for other devices under certain circumstances.

Another provision of SMDA 90 requires manufacturers and distributors to submit medical device reports of certain adverse events related to a device they manufacture or distribute. Specifically, manufacturers and distributors must report to FDA whenever they become aware of information that suggests that a device (1) caused or contributed to a death, serious illness, or serious injury; or (2) malfunctioned, and there is a probability that if the malfunction were to recur, the device would cause or contribute to a death, serious injury, or serious illness. Medical device user facilities such as hospitals, nursing homes, and outpatient treatment facilities are also required to report to FDA serious adverse incidents involving device problems.

Description of Selected Aspects of European Union System for Regulating Medical Devices

This appendix expands on information provided in the report about several features of the EU system for regulating medical devices.

Device Classes

The EU Medical Devices Directive, which covers most devices, established a four-part classification system for medical devices. The rules for classification take into account the riskiness of the device, the device's degree of invasiveness, and the length of time the device is in contact with the body.

- Class I devices are generally regarded as low risk and include most noninvasive products, certain invasive products, and reusable surgical instruments.
- Class IIa devices are generally regarded as medium risk and include both invasive and noninvasive products, generally for short-term use. This class includes some wound dressings; certain products that channel and store blood for administration into the body; surgically invasive devices for transient or short-term use; most active therapeutic devices that administer or exchange energy; and active diagnostic devices that supply energy (other than for illumination) absorbed by the body, such as ultrasonic imagers.
- Class IIb devices are also regarded as medium risk, but this class covers active products therapeutically delivering energy or substances at potentially hazardous levels. Devices placed in this class include blood bags, chemicals that clean or disinfect contact lenses, surgically invasive devices for long-term use, radiological equipment, and condoms and other contraceptive devices (except for intrauterine devices, which are in Class III).
- Class III devices are generally regarded as high risk and include products that are used to diagnose or monitor or that come in contact with the circulatory or central nervous system, such as vascular grafts. This category also includes devices that incorporate medicinal products, such as bone-cement containing an antibiotic.³¹

Conformity Assessment Routes

Under the EU system, the classification of a medical device governs the type of assessment procedure the manufacturer must undertake to demonstrate that the device conforms to the essential requirements in the relevant medical device directive. Generally, when an NB must perform

³¹The EU directive covering active implantable devices does not contain a classification scheme, but the devices governed by that directive are subject to the same review requirements as MDD Class III devices.

aspects of conformity assessment, the manufacturer may choose the assessment route from two or more options.³²

Full Quality Assurance System Review (Annex II)

This type of review examines every aspect of the manufacturer's quality assurance system, covering every phase of the manufacture of a device, from design through shipping. The phases involved in producing a new device for the market include a feasibility phase; design phase, which results in a written definition of the device; design verification, which involves creating prototypes of the device; mass production; and full market release. At each of these phases the manufacturer must ensure that it has defined the requirements for completing that phase and that the "deliverable" for that phase, such as a product design or a packaged device, is verified by qualified staff.

A manufacturer choosing the full QA system route for a Class III device is also required to submit a design dossier for the NB's review. The dossier may include specifications and performance data of the product as claimed; an explanation of how the product meets the essential requirements for safety; risk analysis, including risk control methods; electrical/mechanical/chemical constructional data, including drawings; design verification documents; and, when relevant, clinical investigation data.

After certifying a manufacturer's QA system, the NB must carry out periodic inspections to ensure that the manufacturer is continuing to implement the QA system. Additionally, the NB may pay unannounced visits to the manufacturer to check that the quality system is working properly.

Under the full QA assessment route, the NB does not need to conduct individual reviews of related devices that are produced under the same QA system. If the NB certifies the manufacturer's QA system, that certification covers the related devices. This practice allows the manufacturer to place a CE mark on and market all of the related devices without going through an additional conformity assessment review.

Type Examination (Annex III)

Type examination is a procedure in which the NB ascertains and certifies that a representative sample of the device being reviewed conforms to the essential requirements. The NB reviews documentation on the device that

³²Annex numbers following the names of the assessment routes refer to the sections of the EU medical device directives that describe the various conformity assessment routes.

the manufacturer provides and conducts a product test of the device. The NB physically tests a prototype of the device to determine whether it meets certain standards. The documentation reviewed might include documentation of other product tests. Type examination is always linked with a QA review limited to the production phase of manufacture. The QA review is intended to ensure the consistency of product quality. There are three types of limited QA reviews, as follows.

Product Verification (Annex IV)

In this type of review, the NB must individually test every device produced or test a random sample from every production batch. (This option is also referred to as batch verification.) Few companies choose this approach because it is very expensive.

Production Quality Assurance (Annex V)

Under this type of review, the NB reviews the manufacturer's QA system for the production stage of manufacturing devices, including inspection and QA techniques. The NB must carry out periodic inspections after certifying the production QA system and can pay unannounced visits to the manufacturer. Officials who work with the EU system reported to us that this is the type of production phase quality review that manufacturers select most often to complement type examination.

Product Quality Assurance (Annex VI)

The NB reviews and certifies the manufacturer's system for inspecting and testing final products in an Annex VI review. The NB must carry out periodic inspections and can pay unannounced visits to the manufacturer.

Declaration of Conformity (Annex VII)

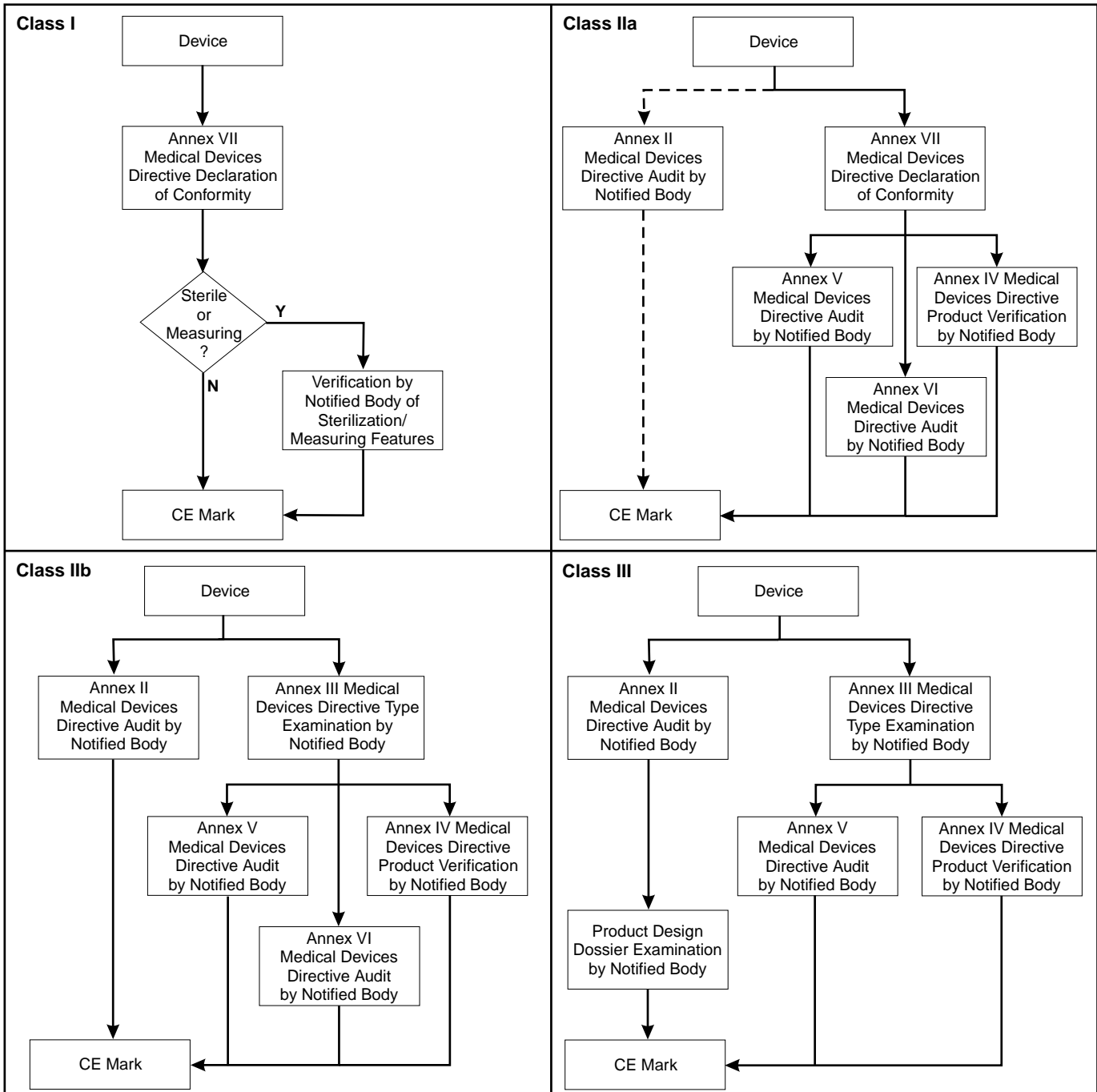
Under this procedure, which is available only for devices in Classes I and IIa, a manufacturer furnishes a declaration that a device conforms to the essential requirements and maintains technical documentation that would permit review of the device.

Assessment Requirements for Device Classes

The EU's MDD specifies which conformity assessment routes each class of devices may use to demonstrate conformity with the essential requirements. Figure III.1 illustrates the assessment routes available to each device class.

Appendix III
Description of Selected Aspects of
European Union System for Regulating
Medical Devices

Figure III.1: Conformity Assessment Routes in European Union Medical Devices Directive



(Figure notes on next page)

Appendix III
Description of Selected Aspects of
European Union System for Regulating
Medical Devices

Source: Medical Devices Agency, Department of Health, UK.

Class I

For Class I products that do not involve measuring devices or sterilization, manufacturers may simply furnish the declaration of conformity (Annex VII) and maintain sufficient technical documentation to permit review of the device. There is no NB review, but the manufacturer must register such devices with the competent authority in the country of the manufacturer's registered place of business. If the device has a measuring function or must be placed on the market in a sterile condition, the manufacturer is also subject to one of the assessment routes covering production quality (Annexes IV, V, or VI). The NB's review focuses only on the measurement or sterilization aspect of the device.

Class IIa

The manufacturer itself may declare conformity with the essential requirements covering the design phase and choose one of the assessment routes covering production quality (Annexes IV, V, or VI). Alternatively, the manufacturer may undergo the full QA system review (Annex II).

Class IIb

The manufacturer may choose either the full QA system review (Annex II), or type examination (Annex III) plus one of the production quality reviews (Annexes IV, V, or VI).

Class III

The requirements are the same as for Class IIb, with two exceptions. If the manufacturer chooses the full QA system review (Annex II), it must also submit a design dossier to the NB. If the manufacturer chooses type examination (Annex III), it must choose either product verification (Annex IV) or production quality assurance (Annex V) for the production phase assessment. Product quality assurance (Annex VI) is not an option for Class III devices.

The Safeguard Clause

The EU's medical device directives have a safeguard clause that requires each member state's competent authority to withdraw from the market CE-marked devices that the competent authority finds may compromise patients' health or safety. The competent authority must immediately inform the European Commission both that it has taken this action and of its reasons for withdrawing the device. If the Commission agrees that the action was justified, it will inform the other member states that the device

Appendix III
Description of Selected Aspects of
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Medical Devices

has been withdrawn. If the Commission believes the withdrawal was unjustified, it informs the competent authority that made the decision and the device manufacturer of that decision. If a competent authority persists in banning a CE-marked product from its country's market, despite the European Commission's decision that the device belongs on the market, the Commission can bring a legal proceeding in the European Court of Justice. European officials view the safeguard clause as a last resort, not something to be invoked routinely. If member states could routinely block the sale of CE-marked devices in their countries, the EU system's goal of facilitating EU-wide trade would be undermined.

Comments From the Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 26 1996

Ms. Sarah F. Jaggard
Director, Health Financing and
Public Health Issues
U. S. General Accounting Office
1 Massachusetts Avenue, N.W.
Room 650
Washington, D.C. 20001

Dear Ms. Jaggard:

Attached are the Food and Drug Administration's comments on the GAO draft report entitled, MEDICAL DEVICE REGULATION: Too Early to Assess European System's Value as Model for FDA.

Sincerely,

for Melinda Plaus
Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Attachment

**Appendix IV
Comments From the Food and Drug
Administration**

Food and Drug Administration Comments on the Draft GAO Report Entitled, MEDICAL DEVICE REGULATION Too Early to Assess European System's Value as Model for FDA.

We have reviewed the report and generally find it to be accurate and complete. The report provides a valuable service by pointing out that

- . the FDA and European Union (EU) systems have different goals, with FDA focusing on public health objectives while the EU system addresses both public health and trade promotion,
- . although both FDA and the EU require devices to be safe, FDA also requires devices to be effective--to have some benefit to the health of patients; the EU requires devices to perform "as intended", but does not require any showing of actual health benefits,
- . the EU system does not evaluate individual devices, but instead evaluates a manufacturer's quality assurance system,
- . there are questions about the independence of notified bodies, most of which are private organizations with client relationships with the manufacturers, and
- . the EU conflict-of-interest standards are less comprehensive than those applied by FDA.

We appreciate GAO's acknowledgement of FDA's efforts "to better manage and streamline its system" and that FDA review times "generally show improvement for applications submitted in fiscal year 1994." The Agency further agrees with GAO that, "[a]t this time there are no data on the experience of the EU device review system that permit meaningful comparison with FDA."

We suggest the following, mostly minor, corrections to the report. As an update for GAO, we also enclose a recent letter from the Director, Center for Devices and Radiological Health to company CEOs regarding FDA's recent progress toward streamlining the approval process.

TECHNICAL COMMENTS

1. At several points the report states that all PMAs require clinical data. Although the vast majority of PMAs require clinical data, there are occasional instances in which clinical data is not required. Section 515(c)(1)(A) of the Federal Food, Drug, and Cosmetic Act requires a PMA application to include "full reports of all information ...

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concerning investigations which have been made to show whether [the] device is safe and effective," but there is no explicit requirement for clinical data per se. Infrequently, an appropriate evaluation is possible using engineering data alone; examples include the stair-climbing wheelchair and dusting powder for surgical gloves.

In one instance, a PMA was approved on the basis of a comprehensive summary of literature concerning the device, a gas used to treat retinal detachment. Although numerous IDE investigations (roughly 70 studies) had been performed with the gas and many were reported in scientific journals, the PMA applicant (the manufacturer of the gas, which is also used in industrial applications) had not sponsored any study of its own. Nevertheless, the literature review and summary was sufficient to demonstrate the safety and effectiveness of the gas and to allow the PMA to be approved.

FDA does not encourage PMA applications without clinical data because even minor changes to a device can sometimes have significant effects on performance. Consequently, FDA has not issued guidance on when it will accept PMAs without clinical data, and deals with any such submissions on a case-by-case basis.

Many PMA supplements do not require clinical data because the changes proposed do not affect safety or effectiveness. As a general rule, clinical data is not needed to make substantial equivalence decisions concerning 510(k)s, but FDA can require submission of clinical data to ensure the new device does not raise different questions of safety and effectiveness than the predicate device.

Now on p. 3.

2. Page 5, 1st full paragraph, second sentence: Change to read, "A medical device can be a product used to cure, prevent, diagnose, or treat illness, provided that its principal intended purposes are not achieved primarily by chemical or metabolic action, such as a pharmaceutical.

Now on p. 3.

3. Page 5, last paragraph, second sentence: Change to read, "... (2) monitoring device manufacturers' compliance with FDA laws and regulations including the Good Manufacturing Practices (GMP) regulation..." There are other laws and regulations that also apply to devices that FDA monitors, as well.

Now on p. 3.

4. Page 6, end of first partial sentence: Add "... or other actions." The post-marketing surveillance data may be used for many other regulatory purposes than just withdrawing a product from the market.

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Now on p. 4.

5. Page 7, first partial sentence: Change to read, "...substantially equivalent to a device already on the market that does not require Class III premarket approval-- called a predicate device."

Now on p. 5.

6. Page 8, footnote 7: Add the following sentence. "The Commission also has the exclusive authority to initiate EU legislation, which must be approved by the European Council, (the principal law-making body) and often the EU parliament."

Now on p. 6.

7. Page 10, 1st partial paragraph, last sentence: Change to read, "For devices regulated as Class III devices, effectiveness includes the additional standard of providing benefit to patients." Add a footnote reading, "Note that the U.S. system does not require absolute proof of safety and effectiveness."

See footnote 9.

8. Page 11, 1st full paragraph, 2nd sentence: Change to read, "FDA's primary mandate is to ensure that devices that reach the public are safe and effective; the agency has secondary statutory responsibility to promote trade in that the Safe Medical Devices Act of 1990 (SMDA) requires the establishment of an Office of International Relations and authorizes the Secretary to enter into agreements with foreign countries to facilitate international trade in medical devices."

See footnote 9.

9. Page 11, footnote 9: Add the following sentence at the beginning of the footnote. "Two sections of the SMDA are relevant. New Section 803 of the FDCA authorizes FDA to enter into agreements with other countries, and amendments to Section 514 allows consideration of trade in setting effective dates for mandatory medical device standards."

Now on p. 7.

10. Page 12, last two complete sentences: Substitute the following paragraphs.

"FDA evaluates the safety and effectiveness of medical devices applications for marketing as required by law. In evaluating the safety and effectiveness of devices that enter the market through the 510(k) route, FDA grants marketing clearance to applications that demonstrate the new device is "substantially equivalent" to a legally marketed predicate device. To obtain this determination, the law requires the manufacturer to demonstrate comparative safety and effectiveness, i.e., that the new device is as safe and effective as the legally marketed predicate device.

"In evaluating the safety and effectiveness of a class III device through the more rigorous premarket approval

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route, the FDA must determine that the application demonstrates there is a reasonable assurance that the device is safe and effective. These criteria must be demonstrated by valid scientific evidence, which include well controlled investigations, studies and objective trials." [A more complete definition of "valid scientific evidence" is in 21 CFR 860.7 (c) (2)]

Now on p. 8.

11. Page 13, 1st full paragraph: Devices reviewed under 510(k) must be at least as safe and effective as the predicate device; valid scientific evidence, as defined by 21 CFR 860.7(c)(2), must support the substantial equivalence decision. Pre-Amendment devices are presumed to be safe and effective except for those specifically classified into class III. Since 510(k) involves a comparative review, each 510(k) substantial equivalence decision builds on the presumption that the predicate device is safe and effective. PMAs involve a stricter standard -- a PMA must establish, independent of any comparison to other devices, that the new device is, in fact, safe and effective. Effectiveness means the same thing in both instances, but is largely presumed for 510(k)s and must be proven for PMAs. If FDA obtains information that a marketed device is not effective for its intended use, FDA can -- and does -- take action to remove the device from the market.

Now on p. 8.

12. Page 13, 1st full paragraph, third sentence: Change the word "policy" to read "practice."

See footnote 17.

13. Page 17, section entitled, Both Systems Link Level of Review to Device Risk: The report notes that both FDA and the EU systems use "risk-based device classification." It would be useful to note here that the two systems apply different sets of controls at each risk level, and individual products or categories of products do not always map to similar controls in the two systems.

Now on p. 11.

14. Page 18, 1st full paragraph, 1st sentence: Change to read, "... released in the U.S. must demonstrate safety and effectiveness,"

Now on p. 12.

15. Page 20, last paragraph, continued on page 21, third and fourth sentences: Change to read, "If a new device has the same intended use and technological characteristics, FDA deems it substantially equivalent to a predicate device and allows the device to be marketed. If a device has new technological characteristics and FDA determines that they do not raise different questions of safety or effectiveness, FDA will find the device to be substantially equivalent to the predicate device. If the device has different technological characteristics and raises different questions of safety and effectiveness, the device will be found not

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substantially equivalent. Sections 513(i)(1)(A) and (B) of the FDCA provide the statutory basis for examining technological characteristics and questions of safety and effectiveness in making substantial equivalence decisions." (Note that this is not a determination that the device is safe and effective.)

Now on p. 13.

16. Page 21, 1st full paragraph, 3rd sentence: Insert the word "may" before the words, "include microbiological" (Note that not all the listed types of studies are required for every application.)

Now on p. 13.

17. Page 21, 1st full paragraph, 4th sentence: Insert the words "may review" before the words, "the results of clinical investigations..."

Now on p. 13.

18. Page 21, last paragraph, continuing on the next page: This discussion should make it clear that a 510(k) review involves a **comparison** of the safety and effectiveness of the predicate with the new 510(k) device (the new device must be as safe and as effective as the predicate), while a PMA must independently establish the safety and effectiveness of the new device.

Now on p. 13.

19. Page 22, 1st full sentence: Change to read, "She also told us that because FDA has chosen to apply a generous interpretation of the scope of the 510(k) requirements..."

Now on p. 14.

20. Page 23, 1st full paragraph, 4th sentence: Insert at the beginning, "Depending on a device's classification". Also, insert the word "may" before the word, "include". For many devices exempted from 510(k) requirements, GMPs are a primary method of assuring safety and effectiveness. Again, the discussion here should make it clear that 510(k) involves a comparison of relative safety and effectiveness, while PMA involves an independent demonstration of safety and effectiveness.

Now on p. 15.

21. Page 25, 1st partial paragraph, last line: Change to read, "... confirmation that a device is as safe and effective as the legally marketed predicate."

See footnote 5.

22. Page 31, 2nd full paragraph: Add a footnote to sentences 2 and 3 stating, "After FDA approves a PMA, a manufacturer may submit an abbreviated application (called a PMA supplement) for FDA approval of certain modifications to the device." You should also define "original PMA."

Now on p. 25.

23. Page 40, 2nd paragraph, 5th and 6th sentences: Change to read, "PMAs and PMA supplements require a more stringent review, and may include the analysis of clinical data to provide a reasonable assurance of safety and effectiveness."

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In addition, manufacturers must comply with certain postmarket requirements such as reporting of certain device-related adverse events."

Now on p. 25.

24. Page 41, 1st paragraph, last sentence: Insert the words, "more rigorous" before the word, "scientific".

See footnote 24.

25. Page 41, footnote: It should be noted that FDA has implemented device performance standards for a number of Class II devices that are radiation-emitting electronic products under the radiological health provisions of the Food, Drug, and Cosmetic Act. Performance standards for radiological devices are codified at--

- . 21 CFR 1010, Performance standards for electronic products; general.
- . 21 CFR 1020, Performance standards for ionizing radiation emitting products.
- . 21 CFR 1030, Performance standards for microwave and radio frequency emitting products.
- . 21 CFR 1040, Performance standards for light-emitting products.
- . 21 CFR 1050, Performance standards for sonic, infrasonic and ultrasonic radiation-emitting products.

Now on p. 26.

26. Page 42, top of page: Change to read, "...present evidence, often including extensive clinical data, that there is a reasonable assurance that a device is safe ..."

Now on p. 26.

27. Page 42, last sentence: Add, "or where it is otherwise appropriate to obtain advice on scientific matters." It would also be more accurate to describe tier II reviews as encompassing the majority of 510(k)s and select PMA **supplements**. An advisory panel is not convened because FDA believes it lacks expertise, but because FDA believes its decision-making would benefit from a wider discussion with users and practitioners.

Now on p. 26.

28. Page 43, second sentence: Change to read, "... legally marketed predicate devices (i.e., being as safe and effective as the predicate device."

Now on p. 27.

29. Page 43, 2nd paragraph, 2nd sentence: Change to read, "... proposed label statements, including statements on promotional materials which describe the device and its use."

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- See footnote 25.
- Now on p. 27.
- Now on p. 27.
- Now on p. 28.
- Now on p. 28.
- Now on p. 28.
- Now on p. 29.
- Now on p. 29.
30. Page 43, Footnote: Delete after b), "... a transitional device, such as injectable silicone, which was regulated as a drug prior to the 1976 amendments," and "post-May 28, 1976..."
 31. Page 44, 2nd sentence: Change to read, "FDA would assess performance testing..." This is not in a regulation as a requirement, therefore, the wording needs to be changed slightly.
 32. Page 45, 2nd paragraph, 1st sentence: Change to read, "Upon completion of the review, the Office of Device Evaluation issues a decision letter..."
 33. Page 46, 2nd paragraph, 2nd sentence: Add at the end, "... or where it is otherwise appropriate to obtain advice on scientific matters."
 34. Page 47, items 3 and 4: Change the word, "decision" to the word, "letter."
 35. Page 47, Last paragraph, 1st sentence: Change to read, "Most original PMAs and a small subset of PMA supplements and 510(k)s require..."
 36. Page 48, 4th and 5th sentences: Change to read, "FDA is not involved in the approval process of the clinical study. If the IRB or FDA determines, however, that the ..." The report should also note that FDA is the final arbiter of whether an investigation is a significant risk (SR) or nonsignificant risk (NSR) study. FDA learns of Institutional Review Board (IRB) NSR decisions through bioresearch monitoring, communications from IRB or other sources, and through other means. Although under 21 CFR 812.66, the IRB is responsible for making the SR-NSR decision, FDA can overrule an IRB's decision. In such cases, an IDE application must be submitted to FDA by the sponsor. Section 520(g)(5) of the FDCA provides FDA with authority to "withdraw an exemption...for a device if [FDA] determines that the conditions applicable to the device...for such exemption are not met." 21 CFR 812.2(b) sets forth abbreviated requirements, and cites 21 CFR 812.20(a) which provides that a sponsor "shall submit an [IDE] application to FDA...if FDA notifies the sponsor that an application is required for an investigation." An IDE may also include data on the design of the device, and data from bench and animal tests.
 37. Page 49, 1st partial paragraph: It should be noted that bioresearch monitoring inspections are conducted during clinical investigations. These inspections help ensure clinical investigations are conducted in accordance with the

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study protocol, thereby assuring the quality and integrity of data and information supporting IDE and PMA applications, and that the rights and safety of study participants are protected. Inspections cover IRB and sponsor oversight, and how clinical investigators conduct the study. Both routine and directed ("for cause") inspections are used. CDRH's bioresearch monitoring program is administered by the Division of Bioresearch Monitoring, Office of Compliance.

Now on p. 30.

38. Page 49, last paragraph: Add the following sentence: "FDA also conducts GMP inspections in conjunction with approval of products."

Now on p. 30.

39. Page 50, 1st paragraph: Add a last sentence reading, "FDA also has discretion to require postmarket surveillance for other devices under certain circumstances."

Now on p. 30.

40. Page 50, 2nd paragraph, 1st sentence: Change to read, "... submit medical device reports of certain adverse events related to a device ..."

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Related GAO Products

Medical Devices: FDA Review Time (GAO/PEMD-96-2, Oct. 30, 1995).

FDA Drug Approval: Review Time Has Decreased in Recent Years
(GAO/PEMD-96-1, Oct. 20, 1995).

Medical Technology: Quality Assurance Systems and Global Markets
(GAO/PEMD-93-15, Aug. 18, 1993).

Medical Technology: Implementing the Good Manufacturing Practices
Regulation (GAO/T-PEMD-92-6, Mar. 25, 1992).

Medical Technology: Quality Assurance Needs Stronger Management
Emphasis and Higher Priority (GAO/PEMD-92-10, Feb. 13, 1992).

Medical Devices: FDA's 510(k) Operations Could Be Improved
(GAO/PEMD-88-14, Aug. 17, 1988).

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