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United States
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Washington, D.C. 20548

159598

Health, Education and Human Services Division

B-278574

November 20, 1997

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Labor and Human Resources
United States Senate

Subject: Medical Devices: European Union's Regulatory Process

Dear Senator Kennedy:

Medical devices are a heterogeneous category of products ranging in complexity from a simple tongue depressor to a sophisticated CT (computed tomography) x-ray system. The Food and Drug Administration (FDA) regulates the manufacture and marketing of tens of thousands of medical devices in the United States. Critics claim that regulatory mechanisms under the European Union's (EU) system are more efficient, and thus faster, and have suggested that elements of the EU approach be adopted as part of a more general reform of FDA. In order to more fully understand the nature of the comparisons being made between the FDA and EU approaches, you requested that we examine the EU system of regulating the entry of medical devices into the marketplace, with a specific focus on product review time. In developing this information, we based our work on a comparison of U.S. and EU regulations and on previous GAO work.[1] We did our work in accordance with generally accepted government auditing standards from July through October 1997.

In summary, we found some differences between the EU and FDA systems that might explain why the EU system may conduct reviews more rapidly than FDA, but at least one difference makes it difficult to reach valid conclusions about the relative speed of review under the two systems.[2]

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[1]See Medical Device Regulation: Too Early to Assess European System's Value as Model for FDA (GAO/HEHS-96-65, Mar. 6, 1996).

[2]There are three major EU legislative provisions covering medical devices–Active Implantable Medical Device Directive, Medical Device Directive, and In Vitro Diagnostics Directive. Our work dealt mainly with the Medical Device

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A manufacturer who seeks to market a medical device in the EU has two general types of choices that can affect the speed of the clearance–the type of procedure used to assess the device and the amount of resources to devote to this assessment. Regarding the first choice, the EU requires an assessment of both the device's design and its manufacturing process to determine whether the device is safe and performs as intended and whether any associated risk is acceptable given the benefits of the device. The manufacturer may choose the type of procedure used to make these assessments. The major decision for the manufacturer is whether to have an evaluation of the device itself or of the process that produces the device. Variations permitted in how the design and the manufacturing process are assessed affect the length of time the assessment takes. In the United States, manufacturers have no choice. The procedure used to clear a device for U.S. marketing depends on the kind of device it is. If a device does not require premarket approval, FDA may clear the product if the manufacturer can show that the new device is "substantially equivalent" in safety and effectiveness to a similar device already on the market. Otherwise, FDA requires that the manufacturer show, through the premarket approval process, that the device is safe and effective.[3]

The second choice available to manufacturers of devices for the EU relates to the amount of resources devoted to the assessment. Manufacturers contract with a third party to conduct the assessment at a cost that is negotiated between the two. For example, a manufacturer willing to devote the resources to hire more reviewers could conceivably obtain a quicker assessment than a manufacturer devoting less resources. In the United States, on the other hand, FDA conducts all reviews and makes all decisions about resources used for product review.[4] (FDA resources are determined by the appropriations process.)

Directive because most devices are regulated under this. Although the Medical Device Directive will not be fully implemented until June 14, 1998, our work focused on the EU system of regulation and how it is expected to work once it is fully implemented and compliance becomes mandatory.

[3]There is also a group of low-risk devices that are exempted from FDA clearance for marketing.

[4]FDA initiated a 2-year pilot program for third-party reviews on August 1, 1996. Under the voluntary pilot program, manufacturers negotiate with FDA-recognized third parties for product review. The fees for the review are negotiated between the manufacturer and third party. Consequently, manufacturers have a choice in resources used for product review.

Although manufacturers' flexibility under the EU system can contribute to more rapid review times, we found that comparisons of review times must be made with caution. In particular, the medical devices assessed under the EU system are likely to be different from those entering review by FDA–that is, many of the assessments that EU conducts are of products that have already been cleared for marketing in the countries where they are sold. Under EU regulation, manufacturers must show that all devices sold–including those already introduced into national markets–conform with EU requirements. Consequently, where the EU requirements are similar to those in countries that are already selling the devices, the EU assessments should be relatively rapid. For such devices, the EU assessment represents a second (and, logically, "easier") review than those conducted by FDA, all of which are of devices that have never been reviewed before.

Additional details about our work are in the enclosure.

AGENCY COMMENTS

We provided a draft of this letter to FDA officials. They agreed with our findings and said that our description of the EU and U.S. approaches in regulating medical devices was "succinct and useful." They agreed in particular that it is difficult to make direct comparisons of review times under the two systems. These officials concurred that many current EU reviews are of products that have already been shown to conform with national requirements in the countries where they are sold, while FDA reviews devices that have never been reviewed before.

FDA officials said that two other factors should be considered when comparing FDA and EU review times. First, while the EU assesses safety and performance for class III products, FDA looks at safety and effectiveness. For example, while the EU would assess whether a laser performs as intended by the manufacturer, FDA would examine whether the indicated use has clinical utility. Thus, they noted, "U.S. clinical trial requirements are considerably more rigorous than the EU requirements." Second, they said that any comparison of review times should take into account the total time required for all review processes necessary to get a product to market. For the EU system specifically, after a device has been found to conform with EU requirements, a second review is required by the reimbursement authority of the country's health care system.

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As agreed with your office, we will make copies of this correspondence available to interested parties. This correspondence was prepared by Bertha Dong and George Silberman. If you or your staff have any questions about this work, please call me at (202) 512-7119 or Ms. Dong at (202) 512-8499.

Sincerely yours,

Bernice Steinhardt
Director, Health Services Quality
and Public Health Issues

EU MEDICAL DEVICE REGULATION AND COMPARISON WITH FDA

In 1985, in response to obstacles in creating a common market, the EU adopted what was termed the "new approach" to medical device regulation. Obstacles included differences in national regulations and the lengthy process for reaching agreement on specific regulations. Under the new approach, countries agree to broad general goals, which are known as "Essential Requirements." Products that conform with these general goals are identified with a CE mark[5] and are marketed throughout the European Economic Area (EEA).[6]

The specific details for achieving the Essential Requirements are found in performance standards.[7] Although conformity with EU performance standards is voluntary, devices that conform with the performance standards are assumed to also conform with the Essential Requirements. Since it is easier to show conformity with specific standards than with general goals, it is expected that manufacturers use the performance standards to show conformity. To illustrate, the Essential Requirement for a sterile product is that it must be sterilized by an appropriate and validated method. The related performance standards specify such technical details as how high the temperature must be and the duration of sterilization.

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[5]The CE mark is a symbol used to indicate that the product complies with the relevant Essential Requirements.

[6]The EEA includes the 15 EU countries and the 3 Economic Free Trade Association (EFTA) members. The EU countries are Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Luxembourg, the Netherlands, Portugal, Ireland, Spain, Sweden, and the United Kingdom. The three EFTA members are Iceland, Norway, and Liechtenstein. These 18 countries constitute a market larger than the size of the United States, Canada, and Mexico combined.

[7]The two EU-designated bodies for standard setting are CEN (European Committee for Standardization) and CENELEC (European Committee for Electrotechnical Standardization). These are nonprofit organizations whose members are the national standards organizations of the EU and EFTA countries. Generally, for medical devices the EU adopted existing international performance standards.

Three major legislative provisions, in the form of EU directives,[8] cover medical devices: the Active Implantable Medical Device Directive,[9] the Medical Device Directive, and the In Vitro Diagnostics Directive. Each is in a different stage of implementation (see table I.1).[10]

Table I.1: EU Medical Device Directive Implementation

Directive	Date adopted by EU	Target date for implementation	Transition period ends
Active Implantable Medical Device Directive	June 20, 1990	January 1, 1993	January 1, 1995
Medical Device Directive	June 14, 1993	January 1, 1995	June 14, 1998
In Vitro Diagnostics Directive	Under development	Anticipated 1998	

We focused on the Medical Device Directive because most medical devices are regulated under it. This directive also covers accessories, components, and software associated with medical devices. It does not cover cosmetics, blood and blood products, and animal and human tissue and their products.

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[8]The manufacture and marketing of medical devices are also regulated by other EU directives. For example, all manufacturers, including medical device manufacturers, are subject to product liability regulations.

[9]The term "active" means having some energy source. For example, a pacemaker is an active implantable device, while a hip replacement is inactive.

[10]Directives, the most common form of EU legislation, need to be transposed into national legislation. After a directive is adopted by the EU members, countries have a period of approximately 18 months in which to transpose the directive into national law. This is followed by a transition period of 2 to 5 years in which both the transposed directive and the preexisting national laws are in effect. During the transition period, manufacturers may elect to comply with either the preexisting national law or the directive. Finally, a specific date is set on which the directive is fully implemented and compliance with the directive becomes mandatory.

At the end of a transition period, all medical devices placed on the market must conform with the Essential Requirements found in the Medical Device Directive.[11] As the EU has no grandfather provision through which device types that have already been introduced into the market can be exempted,[12] this situation has implications for comparing product review times between the EU and FDA. For example, to continue to sell ultrasonic scanners, the manufacturer needs to show that the scanners conform with EU requirements, even though the scanners have already met the national requirements. Where the EU system possesses features similar to those found in preexisting national requirements, like those of the United Kingdom or Germany, the reviews should be relatively rapid. Consequently, unless the review times of medical devices already introduced into the market can be separated from those that have not, product review times under the EU are not comparable with those under FDA.

ESSENTIAL REQUIREMENTS

To market a medical device in the EU, a manufacturer must show that the device conforms with the Essential Requirements. There are two types of requirements—general requirements that apply to all devices and specific requirements that apply only to certain types of devices. For example, there are specific requirements for devices with chemical and biological properties, devices that require sterilization, and those that use radiation. Six Essential Requirements apply to all devices. Basically, the device must be safe, must perform as intended, and the associated risk must be acceptable given the benefits. These six Essential Requirements are

- devices must be designed and manufactured without compromising safety; any associated risk must be acceptable when weighed against benefits;
- design and construction of devices must conform to safety principles, in accordance with the state of the art;
- devices must perform as intended by the manufacturer;
- devices must perform safely and as intended throughout their specified lifetime;
- design, manufacture, and packaging must ensure that safety and performance are not adversely affected by normal transport and storage; and

[11]Devices already in use need not conform with the EU requirements.

[12]The grandfather provision for device types that are already on the market is the basis for the premarket notification, or 510(k) process, used by FDA.

- undesirable side effects must constitute acceptable risk.

In contrast, FDA has two processes, each with distinct requirements, for getting a product on the market–premarket notification, or (510(k)); and premarket approval (PMA). For 510(k)s, manufacturers need to show that the device is "substantially equivalent" in terms of safety and effectiveness to some predicate device already on the market. (Over 90 percent of medical devices cleared by FDA enter the market through the 510(k) process.[13]) The requirements are more stringent for PMAs: Manufacturers need to show that the device is safe and effective.[14] A group of devices that pose little risk is exempt from both the 510(k) and PMA processes. These devices may be subject to such controls as registering the manufacturing site, labeling, appropriately, and adhering to good manufacturing practices.[15]

ASSESSMENT OF CONFORMITY

The applicable procedure for demonstrating conformity with the EU Essential Requirements depends on the classification of the device. The level of regulatory control corresponds with the level of risk posed by the device. Under the EU system, devices are grouped into four classes. The rules for determining the class of a device are listed in the directive, such as whether the device has a therapeutic or diagnostic function, whether it is invasive, and how long it will be in contact with the body. The least risky devices are class I devices, classes IIa and IIb are medium risk devices, and class III devices pose the greatest risk.

FDA also uses different regulatory controls depending on the risk associated with the device. FDA uses three classes with increasing controls from class I to class III devices. All new devices not substantially equivalent to other devices already on the market, however, are subject to the highest level of regulatory control until enough is known about them and their associated risk to reclassify them.

The two systems are more similar than dissimilar in assigning relative risk to medical devices. In table I.2 we provide examples of devices and their respective classifications under the EU and FDA systems.

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[13]About 5 thousand to 7 thousand 510(k)s and 40 to 70 PMAs are submitted to FDA annually.

[14]FDA interprets effectiveness to mean having clinical utility.

[15]Thirty-three percent of all FDA-regulated device types are exempted. It is unclear how many devices on the market fall into these categories.

Table I.2: EU and FDA Medical Device Classification Examples

Medical device	EU classification	FDA classification
Syringe	Class I, reusable surgical instrument; class IIa, invasive and intended to store liquid for infusion	Class I; class II, angiography, infusion pump
Endoscope	Class I, active–uses light to illuminate body, invasive but transient use	Class II, 76 different categories for types of scopes, accessories
Chemical for cleaning medical devices	Class IIa	Class II, ethylene-oxide gas for sterilization
Contact lens	Class IIa	Class II; class III, extended wear soft contact lens
Ultrasonic diagnostic imager	Class IIa, active, diagnostic function	Class II
Cleaning and wetting agents for contact lens	Class IIb	Class III[a]
X ray diagnostic, high voltage generator	Class IIb, active, emits ionizing radiation	Class II
Hip implant	Class IIb	Class II or class III, 27 different categories of implants
Arterial or venous catheters	Class III	Class II, cardiovascular catheter, angiography; class III, coronary angioplasty
Bone cement with antibiotic	Class III	Class III

[a]FDA is in the process of reclassifying these to class II.

In the EU, manufacturers self-certify conformity for most of the least risky, class I devices.[16] Specifically, the manufacturer holds and makes available upon request documentation that shows conformity with the Essential Requirements. For all other classes of device, third-party assessment is required. The greater the potential risk of the device, the greater the role for third-party verification of conformity.

The use of clinical data to show conformity with the Essential Requirements is required only for class III devices.[17] Clinical data can come from existing scientific literature or clinical investigation.[18] That is, scientific literature may exist for medical devices that have been marketed for some time. Manufacturers introducing new technology into the market may need to conduct clinical investigations to generate the necessary clinical data.

For each class, there are different procedures to show conformity and get a CE mark on the product. Manufacturers decide which assessment procedure to use. The major decision is whether to use a type examination or quality system assessment. That is, manufacturers can opt for a review that evaluates the product itself or evaluates the process that produces the product. For a small manufacturer, it may be easier to use the type examination procedure rather than to introduce design controls, process validation, and production controls into the manufacturing process. For a manufacturer with many different types of devices, a quality system assessment may be more efficient. Figures I.1 through I.4 show the applicable conformity assessment procedures by device class.[19]

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[16]Class I devices that have some measuring function or need to be sterilized require third-party assessment.

[17]Clinical data are also required for active implantable devices.

[18]Clinical investigation requires the relevant ethics committee approval for the protection of human subjects within each country. Applications to begin clinical investigation are deemed approved after 60 days unless the government responds otherwise. In contrast, submission for clinical investigations to FDA are deemed approved after 30 days.

[19]The conformity assessment procedures include the following two requirements for manufacturers–they must institute postmarket surveillance and must report adverse events. The EU encourages but does not require members to also institute user reporting of adverse events. Currently, except for countries that have user reporting systems, there is little data to assess how well the countries are able to prevent defective products from entering the market or take defective products off the market.

ENCLOSURE

Figure I.1: Class I Device Conformity Assessment

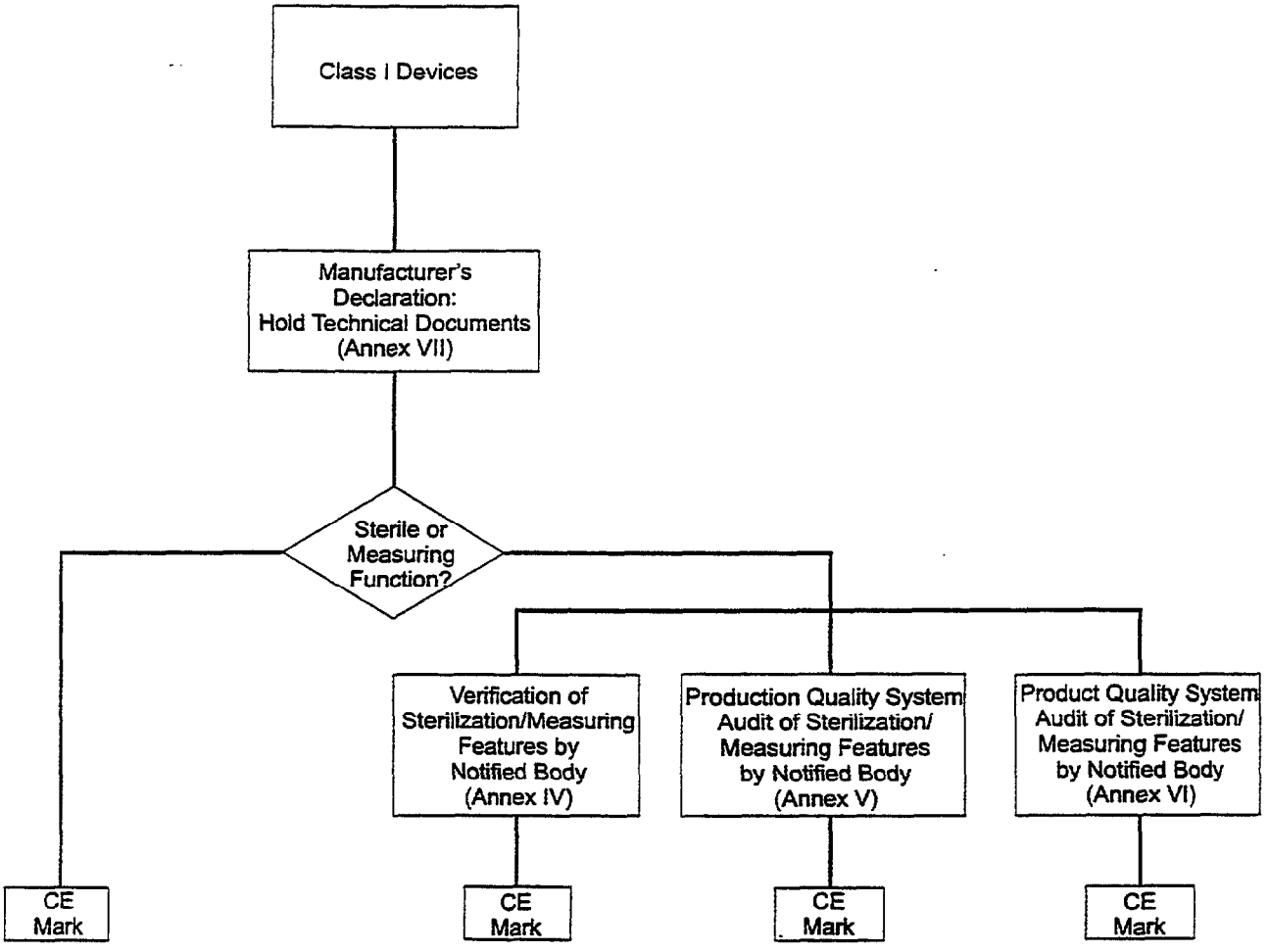


Figure I.2: Class IIa Device Conformity Assessment

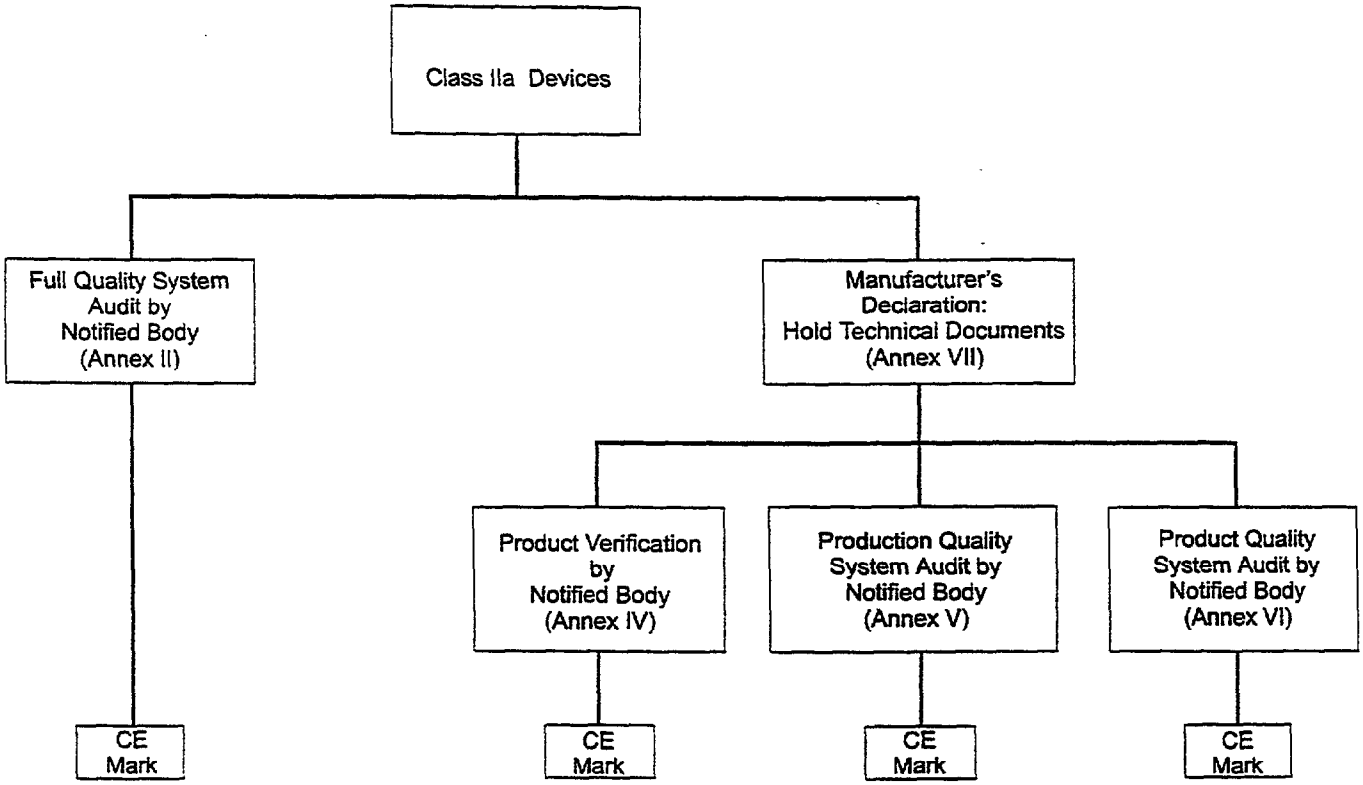
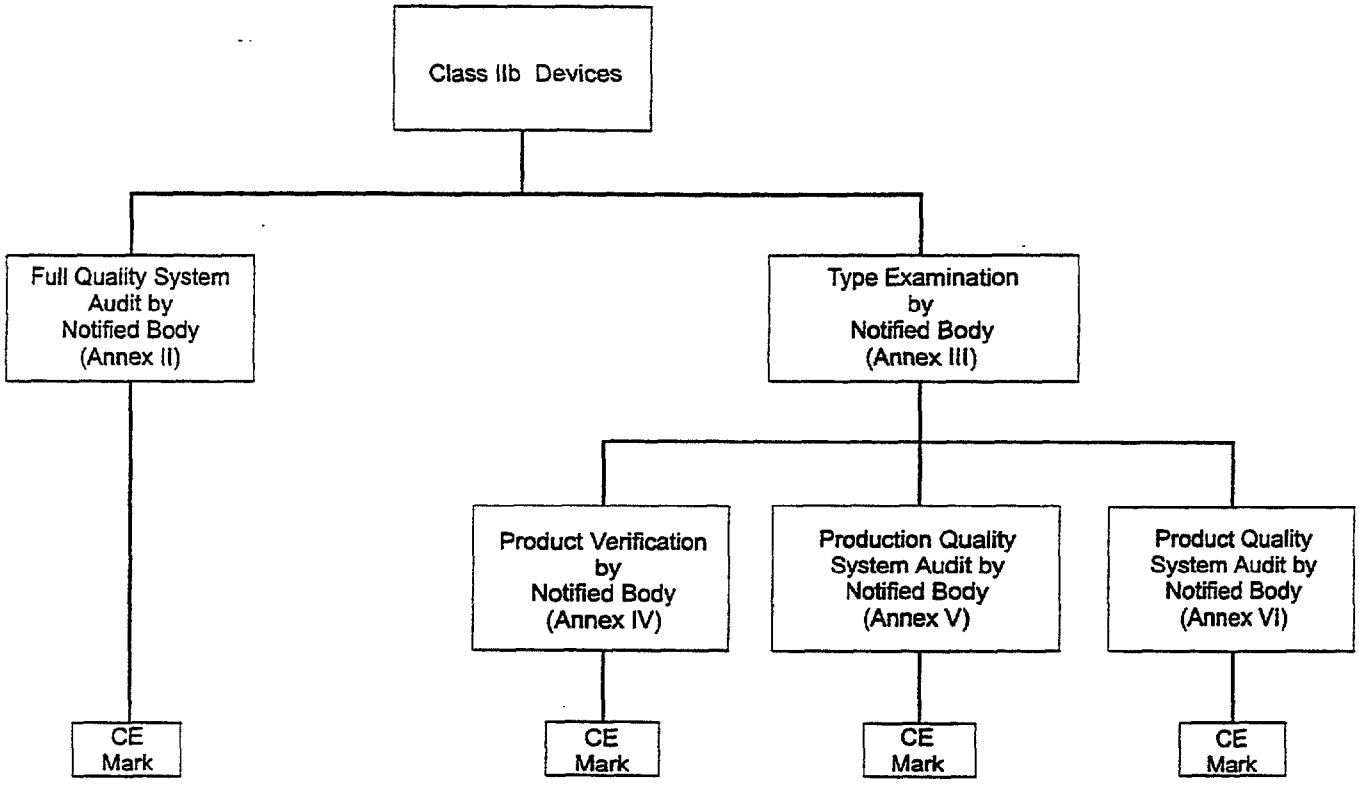
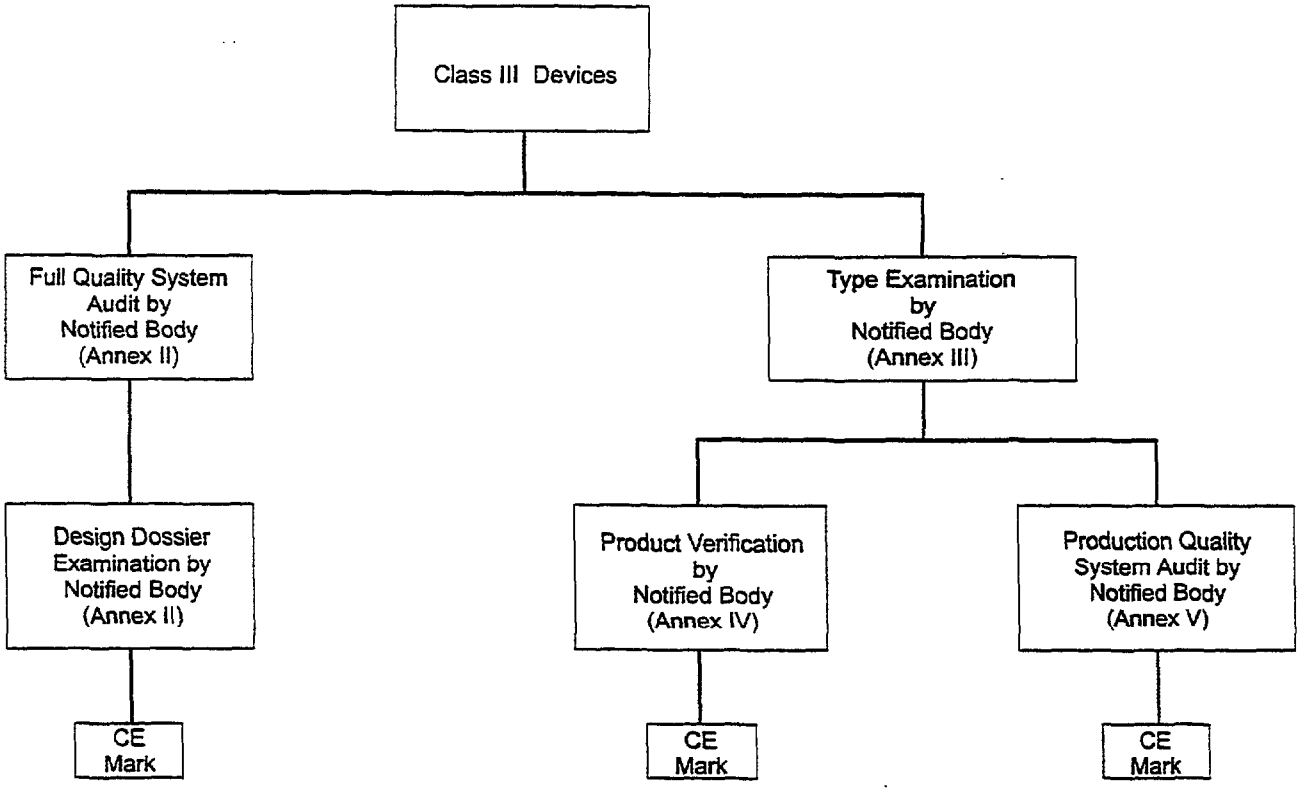


Figure I.3: Class IIb Device Conformity Assessment



ENCLOSURE

Figure I.4: Class III Device Conformity Assessment



The quality system assessment is similar to FDA's Good Manufacturing Practice (GMP) regulations. To harmonize regulations with the EU and other countries, FDA revised its GMP regulations to include preproduction design controls and other features in its harmonized quality system approach.[20]

IMPLEMENTING THE DIRECTIVE

The Medical Device Directive specifies who is responsible for particular functions--government regulators, their "notified bodies" (designated third parties), or manufacturers. The government organization responsible for implementing the directive within each country is called the Competent Authority. Generally, these are the ministries of health or some organization under the ministry. The Competent Authorities also have the power to take appropriate interim measures to withdraw or restrict the marketing of medical devices they deem unsafe; approve clinical investigations and maintain a register of class I device manufacturers; and designate notified bodies and report their identities to the EU.[21]

Notified bodies are the third parties responsible for conducting conformity assessment. Notified bodies can be either private or public organizations[22] and must meet certain minimum requirements listed in the directive.[23] These requirements include independence, professional integrity, professional and technical competence, trained staff, impartiality, liability insurance, and confidentiality. As part of the conformity assessment, notified bodies conduct periodic audits of the manufacturer, including at least one on-site inspection. Notified bodies may also conduct unannounced inspections.

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[20]These revised regulations, renamed Quality Systems Regulations, were effective June 1, 1997.

[21]The EU Commission assigns the notified body a unique identification number, which appears along with the CE mark that manufacturers affix to the medical devices.

[22]Some public notified bodies were government agencies responsible for similar functions prior to the directive--this was the case in France, Italy, Spain, and Portugal. This does not, however, preclude the Competent Authority from designating other private sector notified bodies.

[23]The Competent Authority is responsible for oversight of notified bodies and is responsible for withdrawing the designation if a notified body no longer satisfies the minimum requirements. In addition to the criteria set out in the directive, the EU has performance standards for accrediting and certifying notified bodies.

The manufacturer may contract with any notified body to conduct the conformity assessment. For example, a German manufacturer can select an Italian notified body. Manufacturers negotiate with the notified body on the type of conformance procedure to use and the amount of time to complete the assessment. Once the notified body issues a certificate of conformity, the manufacturer can put a CE mark on the device and market it within the EEA.[24] The manufacturer is responsible for informing the notified body of any changes in the device design or manufacturing process. Depending on the nature of the changes, recertification of the device may be necessary. Manufacturers are also responsible for implementing postmarketing surveillance and reporting adverse events to the relevant Competent Authority.

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[24]The notified body is required, upon request, to inform other notified bodies of conformity certificates issued, refused, or withdrawn.

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